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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002952993 for a patent by THE CORPORATION OF THE TRUSTEES OF THE ORDER OF THE SISTERS OF MERCY IN QUEENSLAND as filed on 29 November 2002.

WITNESS my hand this
Eleventh day of December 2003

A handwritten signature in cursive script, reading "J. Billingsley".

JULIE BILLINGSLEY
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PROVISIONAL SPECIFICATION

for the invention entitled:

"Therapeutic and diagnostic agents"

The invention is described in the following statement:

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THERAPEUTIC AND DIAGNOSTIC AGENTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to therapeutic and diagnostic agents. More particularly, the present invention provides molecules having structural features characteristic of immunoregulatory signalling (IRS) molecules and which are expressed by cells of hematopoietic lineages such as, in particular, leukocytes. The molecules of the present invention find broad application *inter alia* as diagnostic markers for cells, targets for cell therapy and as validated drug targets in order to modulate the immune response and to treat, prevent and diagnose conditions associated with aberrant hematopoietic cell function or activity. The present invention extends to binding partners of the instant molecules such as, for example, antibodies, ligands, adaptor and other signalling associated molecules, agonists and antagonists and to methods of screening for same.

DESCRIPTION OF THE PRIOR ART

Bibliographic details of references provided in the subject specification are also listed at the end of the specification.

Reference to any prior art in this specification is not and should not be taken as an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

The increasing sophistication of recombinant DNA technology is greatly facilitating research and development in a range of biotechnology-related industries. The availability of therapeutic or prophylactic reagents which regulate or manipulate immune responses in the body is developing, based largely on the ability to clone and study molecules which are expressed by cells of the immune system. Cell-surface and secreted molecules are

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particularly important expression products.

The Immunoregulatory Signalling (IRS) family is a group of cell surface molecules which regulate leukocyte function by delivering signals to the cells on which they are expressed. Members of the IRS family are typically either Immunoglobulin gene superfamily members or C-type lectins. Delivery of signals by these IRS molecules is through control of protein phosphorylation. Triggering IRS molecules typically associate with adaptor molecules that contain a cytoplasmic immuno tyrosine based activatory motif (ITAM) which interacts with SH2 domain-containing tyrosine kinases. To-date, a number of common adaptor molecules have been described; CD3 ζ , Fc ϵ R γ , DAP12 and DAP10 (Wilson MJ, Lindquist JA, Trowsdale J: *Immunol Res* 22:21, 2000). These triggering molecules contain either an arginine or lysine residue in the transmembrane region and their expression on the cell surface requires co-expression of the correct adaptor molecule. Inhibitory IRS molecules have one or more tyrosine based inhibitory motif (ITIM) in their cytoplasmic domains which interacts with SH2 domain-containing tyrosine phosphatases.

The leukocyte receptor complex is a large complex of IRS encoding genes on human chromosome 19q13.4 that has been characterized (Wende *et al.*, *Immunogenetics* 51: 703, 2000; Wende *et al.*, *Mamm Genome* 10(2): 154, 1999; Wilson *et al.*, *Methods Mol Biol* 121: 251, 2000; Wagtmann *et al.*, *Current Biol* 7:615, 1997). The complex contains more than twenty genes belonging to the IRS family and includes the genes for the immunoglobulin like transcript (ILT) molecules, the killer Ig-like receptor (KIR) molecules and the natural cytotoxic receptor (NCR) molecule NKp46.

The CMRF-35A and CMRF-35H molecules are also IRS molecules (Clark *et al.*, *Tissue Antigens* 55: 101-109, 2000; Clark *et al.*, *Tissue Antigens* 57: 415-423, 2001; Green *et al.*, *Int Immunol.* 10: 891-899, 1998) having, in the case of CMRF-35H, ITIM in the cytoplasmic region.

35A and 35H are expressed throughout hematopoiesis from the early bone marrow precursors by most leukocyte lineages involved in innate and adaptive immunity. Both

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molecules are members of the Ig superfamily, each having a single V-like extracellular domain. They are most closely related to the Ig binding domains of the Fc receptor for polymeric IgA and IgM (Jackson *et al.*, *Eur. J. Immunol.* 22: 1157-1163, 1992; Green *et al.*, *Int. Immunol.* 10: 891-899, 1998P) but are also distantly related to the TREM molecules (Bouchon *et al.*, *J. Immunol.* 164: 4991-4995, 2000), NKp44 (Vitale *et al.*, *J. Exp. Med.* 187: 2065-2072, 1998) and NKp46 (Pessino *et al.*, *J. Exp. Med.* 188: 953-960, 1998).

Like other IRS molecules, CMRF-35A and CMRF-35H are emerging as molecules which will shed light on how immune cells monitor and respond to their environment. In accordance with the present invention, molecules related to CMRF-35A and CMR-35H have been identified as a family of CMRF-35A and CMRF-35H-like molecules, which are expressed on defined cells and which are encoded by members of a gene family. The term "35-LM" is used in this specification to encompass CMRF-35-like molecules and includes CMRF-35A, CMRF-35H and all other closely related molecules.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ ID NOs: correspond numerically to the sequence identifiers <400>1 (SEQ ID NO:1), <400>2 (SEQ ID NO:2), etc. A summary of the sequence identifiers is provided in Table 2. A sequence listing is provided at the end of the specification.

In accordance with the present invention, a family of closely linked genes on human chromosome 17 has been identified which comprises members encoding polypeptides which are structurally related to the leukocyte surface glycoproteins CMRF-35A and CMRF-35H.

For comparative purposes, the nucleotide and amino acid sequences of human CMRF-35A are set forth in SEQ ID NOs:1 and 2, respectively and the nucleotide and amino acid sequences of human CMRF-35H are set forth in SEQ ID NOs:3 and 4, respectively. In this context, reference to "h" is a reference to a molecule derived from human species; similarly, the prefix "m" is a reference to a molecule derived from mice. The term "35-LM" is used to encompass CMRF-35A, CMRF-35H and related molecules. Table 1 provides a summary of 35-LMs of the present invention.

In one embodiment the present invention provides a nucleic acid molecule or a derivative or homolog thereof corresponding to a gene family which is located on human chromosome 17q22-24 or the equivalent region in other species (e.g. chromosome 11 in mice). The nucleic acid molecules of the present invention, in a further embodiment, encode a polypeptide having one or more of the identifying characteristics of 35A or 35H selected from the following:

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- (i) sequence similarity to an Ig binding domain of CMRF-35A or CMRF-35H;
- (ii) sequence similarity to a cytoplasmic ITIM motif; or
- (iii) expression of polypeptide *in vivo* requires binding to an adaptor molecule comprising an ITAM motif.

The polypeptides may be expressed on the surface of defined populations of hematopoietic cells or may be excreted or be in soluble form.

A homolog includes a nucleic acid molecule comprising a nucleotide sequences having at least 40% similarity or higher to SEQ ID NO:1 (hCMRF-35A) or SEQ ID NO:3 (hCMRF-35H) SEQ ID NO:5 (h35-L1), SEQ ID NO:7 (h35-L2), SEQ ID NO:9 (h35-L3), SEQ ID NO:11 (h35-L4) or SEQ ID NO:13 (h35-L5) or SEQ ID NO:15 (m35a) or SEQ ID NO:17 (m35c) or SEQ ID NO:19 (m35d) or SEQ ID NO:21 (m35f) or SEQ ID NO:23 (m35a) or SEQ ID NO:25 (m35g), or to its complementary form or which is capable of hybridizing to SEQ ID NO:1 or SEQ ID NO:3 or SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11 or SEQ ID NO:13 or SEQ ID NO:15 or SEQ ID NO:17 or SEQ ID NO:19 or SEQ ID NO:21 or SEQ ID NO:23 or SEQ ID NO:25, or its complementary form under low stringency conditions.

In another embodiment, the present invention provides an isolated or recombinant polypeptide derived from the present nucleic acid molecules. In a preferred embodiment, the polypeptides are expressed on the surface of defined populations of hematopoietic cells and conveniently provide cell surface markers for these cell types. In one embodiment, the 35-LMs are expressed on the surface of leukocytes and are capable of influencing the ability of the leukocyte to respond to its environment. Specifically, expression of the 35-LMs influences the ability of the cells to proliferate, differentiate, activate, express cytokines, perform effector functions or undergo apoptosis.

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In yet another embodiment, the polypeptide comprises a sequence of amino acids selected from those set forth in SEQ ID NO:2 (hCMRF-35A) or SEQ ID NO:4 (hCMRF-35H) or SEQ ID NO: 6 (h35-L1) or SEQ ID NO:8 (h35-L2) or SEQ ID NO:10 (h35-L3) or SEQ ID NO:12 (h35-L4) or SEQ ID NO:14 (h35-L5) or SEQ ID NO:16 (m35a) or SEQ ID NO:18 (m35c) or SEQ ID NO:20 (m35d) or SEQ ID NO:22 (m35f) or SEQ ID NO:24 (m35h) or SEQ ID NO:26 (m35g) or an amino acid sequence having at least 20% similarity to all or part of any one of the listed sequences. In another embodiment the instant polypeptide is encoded by a nucleotides sequence set forth in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25 or by a nucleotide sequence having at least about 20% similarity thereto or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25 or its complementary form under low stringency conditions. Binding partners may be used to activate or inhibit the immune system.

In another embodiment, binding partners including soluble forms of the instant polypeptides, antibodies, ligands, agonist and antagonists are usefully developed as diagnostic, therapeutic or prophylactic agents. As targets for cell therapy, the nucleic acid and polypeptide molecules of the present invention provide targets in screens for specific binding partners. Binding partners are contemplated for use in the treatment, prevention or diagnosis of conditions associated with aberrant cellular immunity or altered immune cell function or activity, as is found in cancer, autoimmune conditions, infections, immunosuppression and inflammation, among others.

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TABLE 1
Nomenclature for CMRF-35 family of molecule

FAMILY NAME	NOMENCLATURE	MOUSE ORTHOLOG
35-LM	CMRF-35A	m35h
	CMRF-35H	m35c
	35-L1	m35f
	35-L2	m35d
	35-L3	DIgR1
	35-L4	m35e
	35-L5	m35g DIgR2 m35a

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A summary of sequence identifiers used throughout the subject specification is provided in Table 2.

TABLE 2
Summary of Sequence Identifiers

SEQUENCE ID NO:	DESCRIPTION
1	Nucleotide sequence of hCMRF-35A
2	Amino acid sequence of hCMRF-35A
3	Nucleotide sequence of hCMRF-35H
4	Amino acid sequence of hCMRF-35H
5	Nucleotide sequence of h35-L1
6	Amino acid sequence of h35-L1
7	Nucleotide sequence of h35-L2
8	Amino acid sequence of h35-L2
9	Nucleotide sequence of h35-L3
10	Amino acid sequence of h35-L3
11	Nucleotide sequence of h35-L4
12	Amino acid sequence of h35-L4
13	Nucleotide sequence of h35-L5
14	Amino acid sequence of h35-L5
15	Nucleotide sequence of m35-a
16	Amino acid sequence of m35-a
17	Nucleotide sequence of m35-c
18	Amino acid sequence of m35-c
19	Nucleotide sequence of m35-d
20	Amino acid sequence of m35-d
21	Nucleotide sequence of m35-f
22	Amino acid sequence of m35-f
23	Nucleotide sequence of m35-h
24	Amino acid sequence of m35-h

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SEQUENCE ID NO:	DESCRIPTION
25	Nucleotide sequence of m35-g
26	Amino acid sequence of m35-g
27	Amino acid sequence of m35-e (Ig domain)

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BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a representation of an alignment of the nucleic acid sequences of 35-LMs.

Figure 2 is a representation of an alignment of predicted amino acid sequences of 35-LMs.

Figure 3 is a diagrammatic representation showing the expression analysis of the h35-LMs on cell lines and freshly purified hemopoietic populations.

Figure 4 is a photographic representation showing the expression of AW8 (also called 35-L3) RNA assayed by RT-PCR. Filters are probed with a specific AW8 oligonucleotide. M; marker, 1; B cells, 2; NK cells, 3; granulocytes, 4; monocytes, 5; lin-ve dendritic cells, 6; monocyte derived DC, 7; activated monocyte derived DC, 8; T cells, 9; negative control.

Figure 5 is a representation of an alignment of the nucleic acid sequences of m35-LMs.

Figure 6 is a representation of an alignment of the predicted amino acid sequences of the mouse.

Figure 7 is a diagrammatic representation showing the expression analysis of the m35-LMs on cell lines and freshly purified hematopoietic populations.

Figure 8 is a diagrammatic representation showing the structure the three molecule types in the 35-LM family:-

Type I	=	Inhibitory
Type II	=	E residue in the transmembrane domain
Type III	=	K residue in the transmembrane domain

Figure 9 is a photographic representation showing family expression in various BALB/c tissue, cell lines and sorted spleen cell populations. Pictures show gel photos (dark

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background) and Southernns (light background). (A) to (G) show m35a, m35c, m35e, m35f, m35g, m35h and DIgR1 expression. Expected fragment size is indicated on the right hand side. (H) RT-PCR using mouse GAPDH primers on a selection of cDNA samples with and without (c, control) reverse transcriptase. Integrity of all cDNA samples was confirmed before use for expression analysis. (Thy, thymus; LN, lymph node; BM, bone marrow; Kid, kidney; Hea, heart; Mono, monocytes; Gran, granulocytes).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides members of a new family of immunoregulatory signalling-like molecules encoded by nucleic acid molecules which correspond to a gene family located on human chromosome 17q22-24 or the equivalent region in other species. These molecules are referred to as 35-LMs for "CMRF-35-like molecules".

Accordingly, one aspect of the present invention provides an isolated or recombinant nucleic acid molecule, or a derivative or homolog thereof, corresponding to a gene family which is located on human chromosome 17q22-24 or the equivalent region in other species. The equivalent region in mouse species, for example, is on chromosome 11.

The nucleic acid molecule may be isolated or derived from any suitable animal such as humans, primates, livestock animals (e.g. horses, cows, sheep, donkeys, pigs), laboratory test animals (e.g. mice, rats, rabbits, hamsters, guinea pigs), companion animals (e.g. dogs, cats), or captive wild animals (e.g. deer, foxes, kangaroo). Various databases are now available which compare chromosomal regions of synteny between two species, see for example the Seldin/Debry human/mouse homology map available through OPIM at <http://www3.ncbi.nlm.nih.gov/omim>, among others.

As used herein, the term "derived from" means that a particular element or group of elements has originated from the source described, but has not necessarily been obtained directly from the specified source.

The terms "nucleic acid molecule", "genetic sequence", "sequence of nucleotides" include RNA, cDNA, genomic DNA, synthetic forms and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g. methyl phosphonates, phosphotriesters, phosphoramidates,

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carbamates, etc.), charged linkages (e.g. phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g. polypeptides), intercalators (e.g. acridine, psoralen, etc.), chelators, alkylators and modified linkages (e.g. α -anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence *via* hydrogen binding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule. The nucleic acid molecules of the present invention may be in single, double stranded form and other multiple forms thereof.

Reference herein to a nucleic acid molecule includes reference to a "gene".

The present nucleic acid molecules correspond to a gene family and may be independently or co-ordinately expressed therefrom. The nucleic acid molecules may be full length genes or they may be parts thereof.

The term "gene" is used in its broadest sense and includes cDNA corresponding to the exons of a gene. Reference herein to a "gene" is also taken to include:-

- (i) a classical genomic gene consisting of transcriptional and/or translational regulatory sequences and/or a coding region and/or non-translated sequences (i.e. introns, 5'- and 3'- untranslated sequences); or
- (ii) mRNA or cDNA corresponding to the coding regions (i.e. exons) and 5'- and 3'- untranslated sequences of the gene.

Reference to a "part" of a nucleic acid molecule according the present invention includes fragments of longer molecules defined as having a minimal size of at least about 10 nucleotides or preferably about 13 nucleotides or more preferably 17, 18, 19 or 20 nucleotides. There is no maximal size but a size of about 200 contiguous nucleotides is a useful maximum. Such parts may be useful as probes or primers. Alternatively such molecules may encode a polypeptide such as a soluble protein lacking a cytoplasmic or

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transmembrane domain. Accordingly, this definition includes all sizes in the range of 10-200 nucleotides as well as greater than 200 nucleotides. Thus, this definition includes nucleic acids of 12, 15, 17, 18, 19, 20, 25, 40, 60, 80, 100, 200, 300, 400, 500, 1000 or 1500 nucleotides or nucleic acids having any number of nucleotides within these values (e.g. 13, 16, 23, 30, 28, 50, 72, 121, etc. nucleotides) or nucleic acids having more than 1500 nucleotides or any number of nucleotides between 1500 and the number shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25.

Members of the 35-LM family may be identified or cloned by any of a wide range of strategies including interaction of the polypeptides of the family with specific antibodies, homology cloning, *in silico* mining, through EST database or through further mapping and cloning procedures in relation to the 35-LM genomic complex. A number of strategies also exist for cloning full length cDNAs from the short sequences generated including screening cDNA libraries and 5' and 3' RACE strategies. General teaching on manipulating and cloning nucleic acid molecules may be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, 3rd Edition, 2001).

The isolated or recombinant nucleic acid molecule of the present invention may be deployed in appropriate vectors and cells for sequencing, cloning, expression or for administration to a cell, as described in standard laboratory manuals such as Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons Inc, 1994-1998.

Homologs of the instant nucleic acid sequences include orthologous gene sequences from different species which are related by common phylogenic descent and gene sequences from other species which are similar to the instant nucleic acid molecules as a result of, for example, convergent evolution, wherein the homologs are functionally and structurally related to the instant nucleic acid sequences and are consequently readily identified and/or isolated by hybridization based methods or by sequence comparison

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with available genetic databases. A homolog includes a nucleic acid molecule comprising a nucleotide sequences having at least 40% similarity or higher to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25, or to its complementary form or which is capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25, or its complementary form under low stringency conditions.

The term "similarity" as used herein includes exact identity between compared sequences at the nucleotide or corresponding amino acid level. Where there is non-identity at the nucleotide level, "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. In a particularly preferred embodiment, nucleotide and sequence comparisons are made at the level of identity rather than similarity.

Terms used to describe sequence relationships between two or more polynucleotides or polypeptides include "reference sequence", "comparison window", "sequence similarity", "sequence identity", "percentage of sequence similarity", "percentage of sequence identity", "substantially similar" and "substantial identity". A "reference sequence" is at least 12 but frequently 15 to 18 and often at least 25 or above, such as 30 monomer units, inclusive of nucleotides and amino acid residues, in length. Because two polynucleotides may each comprise (1) a sequence (i.e. only a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of

sequence similarity. A "comparison window" refers to a conceptual segment of typically 12 contiguous residues that is compared to a reference sequence. The comparison window may comprise additions or deletions (i.e. gaps) of about 20% or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by computerized implementations of algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive Madison, WI, USA) or by inspection and the best alignment (i.e. resulting in the highest percentage homology over the comparison window) generated by any of the various methods selected. Reference also may be made to the BLAST family of programs as, for example, disclosed by Altschul *et al.*, *Nucl. Acids Res.* 25: 3389. 1997. A detailed discussion of sequence analysis can be found in Unit 19.3 of Ausubel *et al.*, 1994-1998, *supra*).

The terms "sequence similarity" and "sequence identity" as used herein refers to the extent that sequences are identical or functionally or structurally similar on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a "percentage of sequence identity", for example, is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g. A, T, C, G, I, U) or the identical amino acid residue (e.g. Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. For the purposes of the present invention, "sequence identity" will be understood to mean the "match percentage" calculated by the DNASIS computer program (Version 2.5 for windows; available from Hitachi Software engineering Co., Ltd., South San Francisco, California, USA) using standard defaults as used in the reference manual accompanying the software. Similar comments apply in relation to sequence similarity.

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Preferably, the percentage similarity between a particular sequence and a reference sequence (nucleotide or amino acid) is at least about 30% or at least about 40% or at least about 50% or at least about 65% or at least about 70% or at least about 80% or at least about 90% or at least about 95% or above such as at least about 96%, 97%, 98%, 99% or greater. A percentage identity of approximately 30-32% is particularly preferred.

Similarity at the nucleic acid level may be assessed in assays exploiting different stringency of hybridization conditions as is well known in the art and is, for example, described in Ausubel *et al.*, *supra*, 1994-1998.

Reference herein to stringent hybridization conditions preferably means conditions which permit selective hybridization or annealing between molecules which are substantially similar. The hybridization temperature composition and ionic strength of the hybridization solution which meet this criteria will vary depending upon a number of well characterized factors such as length, degree of complementarity and GC content. For longer sequences it is generally possible to calculate the expected melting point of duplex nucleic acid sequences under various conditions. Hybridization may be to all or part of the instant polynucleotides with the minimum length being sufficient to provide specificity.

Low stringency hybridization conditions includes and encompasses from at least about 0 to at least about 15% v/v formamide and from at least about 1 M to at least about 2 M salt for hybridization, and at least about 1 M to at least about 2 M salt for washing conditions. Generally, low stringency is at from about 25-30°C to about 42°C. The temperature may be altered and higher temperatures used to replace formamide and/or to give alternative stringency conditions.

Medium stringency includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5 M to at least about 0.9 M salt for hybridization, and at least about 0.5 M to at least about 0.9 M salt for washing conditions. High stringency includes and encompasses from at least about 31% v/v to at least about

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50% v/v formamide and from at least about 0.01 M to at least about 0.15 M salt for hybridization, and at least about 0.01 M to at least about 0.15 M salt for washing conditions. In general, washing is carried out $T_m = 69.3 + 0.41 (G+C\%)$. However, the T_m of a duplex DNA decreases by 1°C with every increase of 1% in the number of mismatch base pairs (Bonner and Laskey, *Eur. J. Biochem.* 46: 83, 1974). Formamide is optional in these hybridization conditions. Accordingly, particularly preferred levels of stringency are defined as follows: low stringency is 6 x SSC buffer, 0.1% w/v SDS at 25-42°C; a moderate stringency is 2 x SSC buffer, 0.1% w/v SDS at a temperature in the range 20°C to 65°C; high stringency is 0.1 x SSC buffer, 0.1% w/v SDS at a temperature of at least 65°C.

As used herein, an "isolated" or "substantially pure" nucleic acid molecule (e.g. an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native sequence or protein, e.g. ribosomes, polymerases and many other genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

The present invention further provides recombinant nucleic acids including a recombinant construct comprising all or a part of the present gene family. The recombinant construct may be capable of replicating autonomously in a host cell. Alternatively, the recombinant construct may become integrated into the chromosomal DNA of the host cell. Such a recombinant polynucleotide comprises a polynucleotide of genomic, cDNA, semi-synthetic or synthetic origin which, by virtue of its origin or manipulation: (i) is not associated with all or a portion of a polynucleotide with which it is associated in nature; (ii) is linked to a polynucleotide other than that to which it is linked in nature; or (iii) does not occur in nature. Where nucleic acids according to the invention include RNA, reference to the sequence shown should be construed as reference to the RNA equivalent with U substituted for T. A "recombinant construct" includes an expression construct whereby the nucleotide sequence is expressed to form mRNA. The recombinant construct

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may be RNA or DNA.

Accordingly, recombinant nucleic acids comprising sequences otherwise not naturally occurring are provided by the present invention. Although the wild-type sequence may be employed, it will often be altered, e.g. by deletion, substitution or insertion of one or more nucleotides.

cDNA or genomic libraries of various types may be screened as natural sources of the nucleic acids of the present invention or such nucleic acids may be provided by amplification of sequences resident in genomic DNA or other natural sources, e.g. by PCR. The choice of cDNA libraries normally corresponds to a tissue source which is abundant in mRNA for the desired protein. Phage or plasmid libraries are normally preferred but other types of libraries may be used. Clones of a library are spread onto plates, transferred to a substrate for screening, denatured and probed for the presence of desired sequences.

The nucleic acid molecules of the present invention may be produced by replication in a suitable host cell. Natural or synthetic polynucleotide fragments coding for a desired fragment will be incorporated into recombinant polynucleotide constructs, usually DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the polynucleotide constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction into (with or without integration within the genome) cultured mammalian or other eukaryotic cell lines. The purification of nucleic acids produced by the methods of the present invention are described, e.g. in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989 or Ausubel *et al.*, "Current Protocols in Molecular Biology" John Wiley & Sons Inc, 1992.

The polynucleotides of the present invention may also be produced by chemical synthesis, e.g. by the phosphoramidite method described by Beaucage and Carruthers (*Tetra Letts* 22: 1859-1862, 1981) or the triester method according to Matteucci and Caruthers (*J. Am. Chem. Soc.* 103: 3185, 1981) and may be performed on commercial, automated

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oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

An appropriate promoter and other necessary vector sequences, including selectable markers, will be selected so as to be functional in the host and may include, when appropriate, those naturally associated with the 35-LM gene family. Examples of workable combinations of cell lines and expression vectors are described in Sambrook *et al.*, 1989, *supra* or Ausubel *et al.*, 1992, *supra*. Many useful vectors are known in the art and may be obtained from such vectors as Stratagene, New England Biolabs, Promega Biotech and others. Promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters may be used in prokaryotic hosts. Useful yeast promoters include promoter regions for metallothionein, 3-phosphoglycerate kinase or other glycolytic enzymes such as enolase or glyceraldehyde-3-phosphate dehydrogenase, enzymes responsible for maltose and galactose utilization and others. Vectors and promoters suitable for use in yeast expression are further described in European Patent Publication No. 0 073 675. Appropriate non-native mammalian promoters might include the early and late promoters from SV40 (Fiers *et al.*, *Nature* 273: 113-120, 1978) or promoters derived from murine molony leukemia virus, mouse tumor virus, avian sarcoma viruses, adenovirus II, bovine papilloma virus or polyoma. The CMV promoter is particularly useful in expressing 35-LM genes or cDNA. Insect promoters may be derived from baculovirus. In addition, the construct may be joined to an amplifiable gene (e.g. DHFR) so that multiple copies of the gene may be made. For appropriate enhancer and other expression control sequences, see also *Enhancers and Eukaryotic Gene Expression*, Cold Spring Harbor Press, Cold Spring Harbour, New York (1983). See also, e.g. U.S. Patent No. 5,691,198.

The vectors containing the nucleic acids of interest can be transcribed *in vitro* and the resulting RNA introduced into the host cell by well-known methods, e.g. by injection (see Kubo *et al.*, *FEBS Lett.* 241: 119, 1988), or the vectors can be introduced directly into host

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cells by methods well known in the art, which vary depending on the type of cellular host, including electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; infection (where the vector is an infectious agent, such as a retroviral genome); and other methods. See generally, Sambrook *et al.* (1989) *supra* and Ausubel *et al.* (1992) *supra*. The introduction of the polynucleotides into the host cell by any method known in the art, including, *inter alia*, those described above, will be referred to herein as "transformation". The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

Large quantities of the nucleic acids and polypeptides (see below) of the present invention may be prepared by expressing the 35-LM nucleic acids or parts thereof in vectors or other expression vehicles in compatible prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *E. coli*, although other prokaryotes, such as *Bacillus subtilis* or *Pseudomonas* may also be used.

Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect or amphibian or avian species, may also be useful for production of the proteins of the present invention. Propagation of mammalian cells in culture is *per se* well known. See, Jakoby and Pastan (eds.), *Cell Culture. Methods in Enzymology*, Vol. 58, Academic Press, Inc., Harcour Brace Jovanovich, New York, 1979. Examples of commonly used mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cells, and WI38, BHK and COS cell lines. The Jurkat T-cell line is particularly useful in the practice of this aspect of the present invention. An example of a commonly used insect cell line is SF9. However, it will be appreciated by the skilled practitioner that other cell lines may be appropriate, e.g. to provide higher expression, desirable glycosylation patterns or other features.

Clones are selected by using markers depending on the mode of the vector construction. The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g. by resistance to

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ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

Prokaryotic or eukaryotic cells transformed with the polynucleotides of the present invention will be useful not only for the production of the nucleic acids and polypeptides of the present invention but also, for example, in studying the characteristics of a *35-LM* expression product such as a polypeptide, mRNA, intron and exon.

Antisense polynucleotide sequences are useful in modulating the expression of members of the gene family. Polynucleotide vectors, for example, containing all or a part of the present nucleic acid molecule may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with the target *35-LM* transcription or translation. Furthermore, co-suppression and mechanisms to induce RNAi may also be employed. Such techniques may be useful to selectively inhibit inhibitory *35-LMs* in subjects with for example immunosuppression and may also be useful to inhibit triggering *35-LMs* in subjects with for example inflammatory or autoimmune conditions. Selective inhibition may involve the use of cell or tissue or cell cycle stage specific promoters to regulate expression of the antisense molecules in certain cell types or tissues, or over particular time periods.

Another embodiment of the present invention contemplates an isolated or recombinant nucleic acid molecule corresponding to a gene family which is located on human chromosome 17q22-24 or the equivalent region in another species and comprising a sequence of nucleotides encoding or complementary to a sequence encoding a polypeptide or a nucleotide sequence capable of hybridizing thereto under low stringency conditions wherein said polypeptide exhibits one or more of the identifying characteristics of hCMRF-35A or hCMRF-35H and wherein said polypeptide is expressed on the surface of defined populations of hematopoietic cells.

In a preferred embodiment, the polypeptide comprises a sequence of amino acids selected from those set forth in SEQ ID NO: 6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12,

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SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, or SEQ ID NO:26 or an amino acid sequence having at least 20% similarity to all or part of any one of the listed sequences.

Particularly preferred nucleic acid molecules comprise nucleotide sequences substantially as set forth in SEQ ID NO:5 (h35-L1), SEQ ID NO:7 (h35-L2), SEQ ID NO:9 (h35-L3), SEQ ID NO:11 (h35-L4), SEQ ID NO:13 (h35-L5), SEQ ID NO:15 (m35-a), SEQ ID NO:17 (m35-c), SEQ ID NO:19 (m35-d), SEQ ID NO:21 (m35-f), SEQ ID NO:23 (m35-h), SEQ ID NO:25 (m35-g), or a nucleotide sequence having at least about 15% similarity to all or a part of the sequences or a nucleotide sequence which hybridizes to any of these medium stringency conditions.

The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product, thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 20% similar to the wild-type members of the 35-LM gene family, preferably in excess of 30% or 40% or 60% or 90% or 95%. Also included are proteins encoding by DNAs which hybridize under high or low stringency conditions to 35-LM nucleic acids and closely related polypeptides or proteins retrieved by, for example, antibodies to the 35-LM family member.

The polypeptide molecules may be in isolated and purified form, free or substantially free of material with which it is naturally associated. The polypeptide may, if produced by expression in a prokaryotic cell or produced synthetically, lack native post-translational processing, such as glycosylation. The present invention is also directed to polypeptides which are sequence variants, alleles or derivatives of the 35-LM polypeptides.

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Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein and may be designed to modulate one or more properties of the polypeptide such as stability against proteolytic cleavage without the loss of other functions or properties. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues involved. Preferred substitutions are ones which are conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and tyrosine, phenylalanine.

Certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, epitope-binding regions of antibodies or binding sites on substrate molecules or binding sites on proteins interacting with the 35-LM polypeptide. The interactive capacity and nature of a protein may define that protein's biological functional activity, and certain amino acid substitutions can be made in a protein sequence or its underlying DNA coding sequence and nevertheless obtain a protein with like properties. In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydrophobic amino acid index in conferring interactive biological function on a protein is generally understood in the art (Kyte and Doolittle, *J. Mol. Biol.* 157: 105-132, 1982). Alternatively, the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The importance of hydrophilicity in conferring interactive biological function of a protein is generally understood in the art (U.S. Patent No. 4,554,101). The use of the hydrophobic index or hydrophilicity in designing polypeptides is further discussed in U.S. Patent No. 5,691,198.

The length of the polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues and preferably more than about 35 residues.

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The present invention further contemplates chemical analogs of a 35-LM polypeptide.

Analogues contemplated herein include but are not limited to modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogs.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 ; amidination with methylacetimidate; acetylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH_4 .

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitization, for example, to a corresponding amide.

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

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Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 3.

TABLE 3
Codes for non-conventional amino acids

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α -aminobutyric acid	Abu	L-N-methylalanine	Nmala
α -amino- α -methylbutyrate	Mgab	L-N-methylarginine	Nmarg
aminocyclopropane-	Cpro	L-N-methylasparagine	Nmasn
carboxylate		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-	Norb	L-N-methylglutamine	Nmgln
carboxylate		L-N-methylglutamic acid	Nmglu
cyclohexylalanine	Chexa	L-N-methylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Das	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug

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D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva
D-tyrosine	Dtyr	α -methyl-aminoisobutyrate	Maib
D-valine	Dval	α -methyl- γ -aminobutyrate	Mgabv
D- α -methylalanine	Dmala	α -methylcyclohexylalanine	Mchexa
D- α -methylarginine	Dmarg	α -methylcyclopentylalanine	Mcpen
D- α -methylasparagine	Dmasn	α -methyl- α -naphthylalanine	Manap
D- α -methylaspartate	Dmasp	α -methylpenicillamine	Mpen
D- α -methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
D- α -methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
D- α -methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
D- α -methylisoleucine	Dmile	N-amino- α -methylbutyrate	Nmaabu
D- α -methylleucine	Dmleu	α -naphthylalanine	Anap
D- α -methyllysine	Dmlys	N-benzylglycine	Nphe
D- α -methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
D- α -methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
D- α -methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
D- α -methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
D- α -methylserine	Dmser	N-cyclobutylglycine	Ncbut
D- α -methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
D- α -methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
D- α -methyltyrosine	Dmtv	N-cyclodecylglycine	Ncdec
D- α -methylvaline	Dmval	N-cylcododecylglycine	Ncdod
D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr

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D-N-methylhistidine	Dnmhis	N-(hydroxyethyl)glycine	Nser
D-N-methylisoleucine	Dnmile	N-(imidazolethyl)glycine	Nhis
D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
D-N-methyllysine	Dnmlys	N-methyl- γ -aminobutyrate	Nmgabu
N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmt
D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpn
N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
D-N-methyltyrosine	Dnmtyr	N-methyl- α -naphthylalanine	Nmanap
D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
γ -aminobutyric acid	Gabu	N-(<i>p</i> -hydroxyphenyl)glycine	Nhtyr
L- <i>t</i> -butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
L-ethylglycine	Etg	penicillamine	Pen
L-homophenylalanine	Hphe	L- α -methylalanine	Mala
L- α -methylarginine	Marg	L- α -methylasparagine	Masn
L- α -methylaspartate	Masp	L- α -methyl- <i>t</i> -butylglycine	Mtbug
L- α -methylcysteine	Mcys	L-methylethylglycine	Metg
L- α -methylglutamine	Mgln	L- α -methylglutamate	Mglu
L- α -methylhistidine	Mhis	L- α -methylhomophenylalanine	Mhphe
L- α -methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
L- α -methylleucine	Mleu	L- α -methyllysine	Mlys
L- α -methylmethionine	Mmet	L- α -methylnorleucine	Mnle
L- α -methylnorvaline	Mnva	L- α -methylornithine	Morn
L- α -methylphenylalanine	Mphe	L- α -methylproline	Mpro
L- α -methylserine	Mser	L- α -methylthreonine	Mthr
L- α -methyltryptophan	Mtrp	L- α -methyltyrosine	Mtyr
L- α -methylvaline	Mval	L-N-methylhomophenylalanine	Nmhph

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N-(N-(2,2-diphenylethyl)	Nnbhm	N-(N-(3,3-diphenylpropyl)	Nnbhe
carbamylmethyl)glycine		carbamylmethyl)glycine	
1-carboxy-1-(2,2-diphenyl-	Nmbc		
ethylamino)cyclopropane			

Crosslinkers can be used, for example, to stabilize 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with $n=1$ to $n=6$, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition, peptides can be conformationally constrained by, for example, incorporation of C_α and N_α -methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and the N or C terminus.

The term "peptide mimetic" or "mimetic" is intended to refer to a substance which has the essential biological activity of the 35-LM family member polypeptide. A peptide mimetic may be a peptide-containing molecule that mimics elements of protein secondary structure. The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions such as those of antibody and antigen, enzyme and substrate or scaffolding proteins. A peptide mimetic is designed to permit molecular interactions similar to the natural molecule. A mimetic may not be a peptide at all, but it will retain the essential biological activity of a natural 35-LM polypeptide.

The present invention is particularly useful, therefore, for screening compounds by using one or more 35-LM family member polypeptide or binding fragment thereof in any of a variety of drug screening techniques, such as those described herein and in International Publication No. WO 97/02048.

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The 35-LM family member polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, or borne on a cell surface. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant polynucleotides expressing the polypeptide or fragment, preferably in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between a polypeptide or fragment and the agent being tested, or examine the degree to which the formation of a complex between a 35-LM polypeptide or a part thereof and a specific antibody is aided or interfered with by the agent being tested.

Polyclonal antibodies may conveniently be used, however, the use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production is derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation (i.e. comprising 35-LM polypeptide) or can be done by techniques which are well known to those who are skilled in the art. (See, for example, Douillard and Hoffman, Basic Facts about Hybridomas, in *Compendium of Immunology* Vol. II, ed. by Schwartz, 1981; Kohler and Milstein, *Nature* 256: 495-499, 1975; Kohler and Milstein, *European Journal of Immunology* 6: 511-519, 1976). Single chain antibodies or transgenic mice expressing humanized antibodies or other recognition proteins may also be used. Useful proteins in this regard include diabodies, peptide mimetics and antibody fragments such as scFv fragments and Fab fragments.

Monoclonal antibodies which bind specifically to members of the 35-LM family provide a convenient method for detecting and targeting the cells which express one or more 35-LM. For detecting one or more cells expressing particular 35-LMs either alone or in conjunction with other cell surface molecules, an large number of assays are available. For example, populations of cells may be routinely assessed for their 35-LM polypeptide cell surface markers using identifiable polypeptide specific binding partners such as primary antibodies

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to cell surface markers and secondary antibodies labeled with detectable markers. Antibodies may further differentiate between allelic or altered forms of 35-LM polypeptides. The presence of members of the 35-LM members may be accomplished in a number of ways such as by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by reference to U.S. Patent Nos. 4,016,043, 4,424,279 and 4,018,653. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target. Monoclonal antibodies may be used as agonists or antagonists of 35-LM polypeptide activity. They may also be formulated as a composition suitable for administration to an individual in a method of treatment or prophylaxis.

The antibodies of the present invention are useful in a range of other methodologies including flow cytometry, which typically detects optical parameters. For example, a flow cytometer may be used to determine forward scatter (which is a measure of size of a carrier), side scatter (which is sensitive to refractive index and size of a particle [see Shapiro, *"Practical flow cytometry"*, 3rd ed. Brisbane, Wiley-Liss, 1995]) and fluorescent emission.

As is known in the art, flow cytometry is a high throughput technique which involves rapidly analyzing the physical and chemical characteristics of cells or other particles as they pass through the path of one or more laser beams while suspended in a fluid stream. As each cell or particle intercepts the laser beam, the scattered light and fluorescent light emitted by each cell or particle is detected and recorded using any suitable tracking algorithm.

A modern flow cytometer is able to perform these tasks up to 100,000 cells/particles s⁻¹. Through the use of an optical array of filters and dichroic mirrors, different wavelengths of fluorescent light can be separated and detected simultaneously. In addition, a number of lasers with different excitation wavelengths may be used. Hence, a variety of fluorophores can be used to target and examine, for example, intra- and extra-cellular properties of

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individual cells. The scattered light measurements can also classify an individual carrier's size, shape, granularity and/or complexity and, hence, belonging to a particular population of interest (Shapiro, 1995, *supra*).

Suitable flow cytometers which may be used in the methods of the present invention include those which measure five to nine optical parameters (see Table 4) using a single excitation laser, commonly an argon ion air-cooled laser operating at 15 mW on its 488 nm spectral line. More advanced flow cytometers are capable of using multiple excitation lasers such as a HeNe laser (633 nm) or a HeCd laser (325 nm) in addition to the argon ion laser (488 or 514 nm). Optical parameters, corresponding to different optically detectable/quantifiable attributes, for a carrier, may be measured by a flow cytometer to provide a matrix of qualitative and/or quantitative information, providing a code (or addressability in a multi-dimensional space) for the carrier.

TABLE 4

Exemplary optical parameters which may be measured by a flow cytometer.

Parameter	Acronym	Detection angle form incident laser beam	Wavelength (nm)
Forward scattered light	FS	2-5°	488*
Side scattered light	SS	90°	488*
"Green" fluorescence	FL1	90°	510-540 [†]
"Yellow" fluorescence	FL2	90°	560-580 [†]
"Red" fluorescence	FL3	90°	>650 [#]

* using a 488 nm excitation laser

[†] width of bandpass filter

[#] longpass filter

For example, Biggs *et al.* (*Cytometry* 36: 36-45, 1999) have constructed an 11-parameter flow cytometer using three excitation lasers and have demonstrated the use of nine distinguishable fluorophores in addition to forward and side scatter measurements for purposes of immunophenotyping (i.e. classifying) cells. The maximum number of

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parameters commercially available currently is 17: forward scatter, side scatter and three excitation lasers each with five fluorescence detectors. Whether all of the parameters can be adequately used depends heavily on the extinction coefficients, quantum yields and amount of spectral overlap between all fluorophores (Malemed *et al.*, "*Flow cytometry and sorting*", 2nd Ed., New York, Wiley-Liss, 1990). However, it will be understood that the present invention is not restricted to any particular flow cytometer or any particular set of parameters. In this regard, the invention also contemplates use in place of a conventional flow cytometer, a microfabricated flow cytometer as, for example, disclosed by Fu *et al.* (*Nature Biotechnology* 17: 1109-1111, 1999).

A flow cytometer with this capacity to sort is known as a "fluorescence-activated cell sorter" (FACS). Accordingly, the step of sorting in the present method of obtaining a population of detectably unique carriers may be effected by flow cytometric techniques such as by fluorescence activated cell sorting (FACS) although with respect to the present invention, FACS is more accurately "fluorescence activated carrier or solid support sorting" (see, for example, "*Methods in Cell Biology*" Vol. 33, Darzynkiewica, Z. and Crissman, H.A., eds., Academic Press) and Dengl and Herzenberg, *J. Immunol. Methods* 52: 1-14, 1982.

The present invention further relates to modified antibodies. Modified antibodies of particular interest are single chain fragments carrying the variable (V) region of an antibody. This is called an scFv antibody fragment. scFv antibody fragments are derived from Fragment antigen binding (Fab) portions of an antibody and comprise only the V region of a heavy chain linked by a stretch of synthetic peptide to a V region light chain.

In a particularly preferred embodiment, antibodies may also be used to purge target cells, either alone or in conjunction with other immune or cytotoxic molecules.

35-LM expression and variation may also be assessed at the nucleic acid level. For example RT-PCR based methods may be employed to monitor expression of nucleic acid molecules in different cell types and tissues. Nucleic acid sequence variation may be

detected by direct DNA sequencing, either manual sequencing or automated fluorescent sequencing, can detect sequence variation. Another approach is the single-stranded conformation polymorphism assay (SSCP) [Orita *et al.*, *Proc. Nat. Acad. Sci. USA* 86: 2776-2770, 1989]. This method can be optimized to detect most DNA sequence variation. The increased throughput possible with SSCP makes it an attractive, viable alternative to direct sequencing for mutation detection on a research basis. The fragments which have shifted mobility on SSCP gels are then sequenced to determine the exact nature of the DNA sequence variation. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE) [Sheffield *et al.*, *Am. J. Hum. Genet.* 49: 699-706, 1991], heteroduplex analysis (HA) [White *et al.*, *Genomics* 12: 301-306, 1992] and chemical mismatch cleavage (CMC) [Grompe *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 5855-5892, 1989]. Other methods which might detect mutations in regulatory regions or which might comprise large deletions, duplications or insertions include the protein truncation assay or the asymmetric assay. A review of methods of detecting DNA sequence variation can be found in Grompe [*Nature Genetics* 5: 111-117, 1993]. Once a mutation is known, an allele specific detection approach such as allele specific oligonucleotide (ASO) hybridization can be utilized to rapidly screen large numbers of other samples for that same mutation. Such a technique can utilize probes which are labeled with gold nanoparticles to yield a visual color result [Elghanian *et al.*, *Science* 277: 1078-1081, 1997]. Techniques are available to screen RNA products or proteinaceous products.

Preferably, the polypeptides encoded by the present nucleic acid molecules are expressed on the surface of defined populations of hematopoietic cells. Cells of leukocyte lineages are contemplated, including, for example, monocytes, dendritic cells, NK cells, granulocytes, T-lymphocytes, B-lymphocytes, monocyte derived dendritic cells and precursors thereof.

The phrase, "differentially expressed" is a broad reference to expression of mRNA or a polypeptide in a particular cell type, organ or tissue, stage of development, differentiation cell cycle, or, wherein expression is varied as a result of age, infection, immune or other

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status or an individual.

The present invention provides methods of screening for agents which interact with the 35-LM nucleic acid molecules or polypeptides of the present invention. Competitive binding assays are preferred. Conveniently, high throughput screening of test peptides is used to identify peptides with suitable affinity and selectivity. Purified 35-LM polypeptide may be immobilized on cells or membranes expressing 35-LM polypeptide may be employed.

Following identification of antibodies or natural or artificial agonists and antagonists including scFv fragments, one or more substances may be manufactured or formulated as a composition suitable for administration to individuals in a method of treatment or prophylaxis.

Such compositions can be formulated according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing, Company, Easton, PA, U.S.A.). The composition may contain the active agent or pharmaceutically acceptable salts of the active agent. These compositions may comprise, in addition to one of the active substances, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. intravenous, oral, intrathecal, epineural or parenteral. For antibodies, parenteral administration is particularly useful.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and

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the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, International Patent Publication No. WO 96/11698.

For parenteral administration, the compound may dissolved in a pharmaceutical carrier and administered as either a solution of a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

The active agent is preferably administered in a therapeutically effective amount. The actual amount administered and the rate and time-course of administration will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc. is within the responsibility of general practitioners or specialists and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical Sciences, supra*.

Instead of administering these agents directly, they may also be produced in the target cell, e.g. in a viral vector or in a cell based delivery system such as described in U.S. Patent No. 5,550,050 and International Patent Publication Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. The vector could be targeted to the target cells. The cell based delivery system is designed to be implanted in a patient's body at the desired target site and contains a coding sequence for the target agent. Alternatively, the agent could be

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administered in a precursor form for conversion to the active form by an activating agent produced in, or targeted to, the cells to be treated. See, for example, European Patent Application No. 0 425 731A and International Patent Publication No. WO 90/07936.

The present invention is further described by the following non-limiting Examples.

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EXAMPLE 1

Identification of CMRF-35 family members

cDNA probes specific for CMRF-35A and CMRF-35H Ig domains were identified as binding to a large number of independent, non-overlapping PAC clones. Partial and full length cDNA molecules which map to human chromosome 17q22-24 were identified from EST and 5' RACE studies. Alignment of the sequences with CMRF-35A and CMRF-35H indicated similarities over the transmembrane region. cDNA and gDNA sequences were also used to further RT-PCR based expression studies. An alignment of the nucleic acid sequences of the human cDNAs is shown in Figure 1. An alignment of the protein sequences of the human cDNAs is shown in Figure 2.

An RT-PCR assay was established to characterize the expression of the novel members of the 35-LM family in normal hematopoietic lineages and cell lines. Screening of public and commercial databases was used to confirm that the EST used for the RT-PCR represents a single exon. The sequence of the complete cDNAs is used to design RT-PCR primers that cross intron-exon junctions. The primers are used to confirm the expression data. This ensures the identification of any splice variants.

EXAMPLE 3

Expression studies for CMRF-35

Figure 3 summarizes the expression analysis of the h35-LMs on cell lines and freshly purified hematopoietic populations.

RT-PCR was performed to determine the expression of h35-L3 (AW8) on cDNA made from RNA isolated from hematopoietic cell lines (leukemic derived) and cells of different hematopoietic lineages. Analysis of hematopoietic cell line data indicate that 35-L3 is expressed by the derived cell lines HEL, HL60, KG-1, Monomac 6, U937 and K562 and the Hodgkins disease derived cell lines HDLM-2 and KM-H2. 35-L3 was not found in lines of T or B cell origin. The RNA for this molecule is predominantly expressed by cells

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of the myeloid lineage as shown in Figure 4. Further analysis of dendritic cell populations indicate that 35-L3 (AW8) is expressed only by the CD11c⁺ myeloid derived DC and not the CD11c⁻ lymphoid derived DC. Thus, in addition CD33, CD13, and CD14 this molecule appears to be expressed by cells of the myeloid lineage. The inventors have shown that 35-L3 is expressed by leukemic cells from single AML patients. Blast cells from a patient newly diagnosed with AML was selected by flow sorting. RNA isolated from these cells, when used in RT-PCR show the expression of the CMRF-35-L3 specific PCR products.

EXAMPLE 4

Homologs of hCMRF-35 molecules

To locate mouse homologs of h35-LM (i.e. murine orthologs), a series of searches were conducted in the public and commercial databases around the region 11 E2.

Initially, six computationally predicted genes sharing significant homology with h35-LMs were chosen for further analysis. These genes were termed m35a, m35c, m35d, m35f and m35g. Of these, m35a, m35d and m35f contained complete coding regions. Comparison to mouse ESTs in NCBI provided overlapping sequences from which a complete coding sequence could be obtained for m35c and m35g. The ESTs were as follows: 3' end of m35c (gi: 16445999) and middle region of m35g (EST gi: 15562326).

Further database searches revealed two new homologs termed m35h and DIgR2 (86% similar to DIgR1) with NCBI Accession Nos. XM_126721 and XM_126696. Only m35h contained a complete coding region.

The alignment of the nucleic acid sequences of the mouse cDNAs is shown in Figure 4 and the alignment of the protein sequences of the mouse cDNAs is shown in Figure 5.

EXAMPLE 5***Expression analysis of mouse homologs***

To study the expression of m35a, m35c, m35d, m35e, m35f, m35g, m35h and DIgR1 in cell lines and freshly prepared haemopoietic cell populations, primers were designed that were specific for each transcript and cross-checked for sequence similarity against other family members. DIgR1 was included for comparison to published data (Luo *et al.*, *Biochem. Biophys. Res. Commun.* 287: 35-41, 2001). Optimization of RT-PCR conditions was necessary before analysis of expression could be performed (Table 5).

TABLE 5***Optimization of RT-PCR conditions****

	m35a	m35c	m35d	m35e	m35f	m35g	m35h	DIgR1
A								
	Optimal RT-PCR conditions	AT: 60°C	AT: 60°C	AT: 60°C	AT: 60°C; 3' primer: 10 mM	AT: 60°C	Touchdown MgCl ₂ : 2.0 mM	AT: 60°C
	RT-PCR fragment size	239	266	159	217	142	111	244
B								
	Ig domain RT-PCR conditions	AT: 65°C	AT: 65°C	AT: 65°C	AT: 64°C; 3' primer: 10 mM	AT: 53°C	na	na
	Ig RT-PCR fragment size	444	447	393	405	462	na	na

* (A) refers to RT-PCRs used for expression analysis while (B) refers to RT-PCRs used for amplification of Ig domains. Only annealing temperature (AT) for RT-PCRs are indicated, unless the PCR cycle varied from standard conditions.

Optimization involved performing a temperature gradient RT-PCR on each primer set, which altered the annealing temperature between 50°C and 65°C. If multiple products were amplified making interpretation difficult, MgCl₂ concentrations were titrated between 1.5 mM and 3.5 mM. Further optimization was necessary for m35e, which involved varying forward and reverse primer concentrations and m35h, which involved designing a

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touchdown RT-PCR program. The touchdown program contained an initial denaturation of 94°C for 5 min, followed by 20 cycles of [94°C for 15 sec; 65°C for 15 sec - 0.5°C/cycles; 72°C for 1 min], then 15 cycles of [94°C for 15 sec; 55°C for 15 sec; 72°C for 1 min] and a final extension of 72°C for 5 min. This cycles prevents early false priming, while facilitating amplification, by lowering the annealing temperature in later stage of the program.

The expression of m35a, m35c, m35d, m35e, m35f, m35g, m35h and DlgR1 was examined by RT-PCR and Southern blotting (Figure 9 and Figure 7). Amplified template included cDNA synthesized from selected tissues of BALB/c mice, mouse cell lines, C57BL/6 mouse spleen cell subsets and bone marrow derived DCs. Expression of m35-LMs in tissue was generally widespread with only m35d and m35f showing restricted expression for lymphoid tissue. m35a, m35c and DlgR1 were expressed in all tested tissues and m35e and m35h were negative only in skin. Spleen was the only tissue positive for all family members.

EXAMPLE 6

Characterization of the molecular structure of a novel myeloid restricted molecule, 35-L3

Preliminary studies identified the partial sequence of the 35-L3 molecule from an EST database (AW880126). The gene for the molecule has been localized to human chromosome 17. The inventors have established an RT-PCR that identifies this molecule and shows that it is an expressed product. The PCR product has been cloned and sequenced, confirming its identity as the 35-L3 EST. 5' and 3' RACE protocols were used to further identify the full length molecule. PBMC cDNA library in an expression vector, pCMV-SPORT.6 (Life Technologies) is used to isolate a full length clone. PCR and hybridization screening is used. The full length 35-L3 molecule (cDNA) sequence corresponds to an ORF with sequence similarity to the CMRF-35A and CMRF-35H sequences which, in accordance with the present invention, is identified on chromosome 17.

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The isolated cDNA(s) is sequenced by Big Dye chain termination sequencing. The 5' RACE data are used to confirm that a full clone has been isolated. The complete sequence of the cDNA is used to analyze the 35-L3 gene structure. Two sequence BLAST searches are performed using the 35-L3 cDNA sequence and the chromosome 17 sequence. This will provide the sequence of the putative promoter region.

RT-PCR has been used to establish the expression of the 35-L3 EST in normal haemopoietic lineages and cell lines. This RT-PCR was designed from a single EST. Screening of the public databases indicates that this EST represents a single exon. The sequence of the complete cDNA is used to design RT-PCR primers that cross intron-exon junctions. These primers are used to confirm the expression data. This will ensure that any splice variants are identified. Variants identified are characterized at the molecular level to determine the presence of alternative exon usage.

EXAMPLE 7

***To express 35-L3 and generate monoclonal antibodies (mAb) to
35-L3 to study its expression in leukocytes and other tissues***

Constructs are made to allow expression of recombinant forms of the 35-L3 molecule in mammalian and prokaryotic systems. The cDNA isolated from the pCMV-SPORT library is inserted in an expression vector. This is used to transiently transfect COS cells. Mice are immunized using a tolerance procedure (Dzionic *et al.*, *J Immunol* 165(11): 6037, 2000) that allows the induction of tolerance to the parental COS cells, whilst immunizing against the transfected cells. Expression of the cDNA is monitored by RT-PCR and Northern blotting to ensure at least RNA is transcribed. DNA immunization was also used in place of the tolerance procedure.

The cDNA sequence is used to design PCR primers to produce a range of fragments that is used to make recombinant proteins. These include the potential extracellular domains of the 35-L3 molecule fused to (1) the human IgG1 Fc portion, (2) a HIS tag or (3) a myc tag.

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The fusion products are expressed in mammalian cells or *E. coli* as appropriate. The fusion proteins will be purified by affinity chromatography using protein A for IgG1 Fc fusion proteins, and anti-His or anti myc monoclonal antibodies as appropriate. Purified recombinant proteins are monitored by SDS-PAGE.

The recombinant proteins are used to immunize rabbits to produced rabbit polyclonal serum. Recombinant proteins or cDNA in expression vectors are used to immunize mice to produce mAb. Specific mAb are identified by ELISA using the recombinant fusion proteins or by flow cytometry using RT-PCR expression data to determine appropriate cell lines as targets.

The mAb is used to analyze the expression of the 35-L3 molecule on normal haemopoietic populations by flow cytometry. Basic biochemical characterization (immunoprecipitation or Western Blots) of the 35-L3 molecule is performed to identify its molecular size.

EXAMPLE 8

To analyze 35-L1 to L5 expression in leukemias

Blast populations are isolated from bone marrow or peripheral blood samples of new and relapsed AML and ALL patients. A standard cell surface phenotype of the leukemic cells are determined and this is used in three color analysis to phenotype the cells. If necessary, the leukemic cells are sorted for more detailed phenotypic analysis.

Aliquots of 5 ml peripheral blood is collected from newly diagnosed leukemic patients according to ethical consent. Patients of each subtype is tested and reported according to the new classification.

In addition, sorted blast cells are used to prepare RNA and cDNA for quantitative real time (RT) polymerase chain reaction (PCR) analysis. This allows information to be collected on the expression of the 35-L1, 35-L2, 35-L3, 35-L4 or 35-L5 (referred to as "35-L1 to L5") prior to the generation of monoclonal or polyclonal reagents.

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EXAMPLE 9

Functional aspects of 35-L1 to L5 specific mAb

Given the potential of this molecule to be used, for example, as a marker for leukemic cells, mAbs generated herein are assessed for their ability to target or purge 35-L1⁺ to L5⁺ cells. Reference to "35-L1 to L5" means any one of 35-L1, 35-L2, 35-L3, 35-L4 or 35-L5 or combinations thereof. The following experiments are performed to assess their potential:

- (a) to deliver intracellular toxins or radionucleotides *via* internalization;
 - (b) to effect the growth of 35-L1⁺ to L5⁺ cells in culture; and
 - (c) their ability to target and lyse 35-L1⁺ to L5⁺ and homolog bearing cells.
-
- (a) The ability of the mAb bound to surface 35-L1⁺ to L5⁺ to internalize. Biotinylated mAb will be bound to 35-L1⁺ to L5⁺ targets. Cells are incubated at 37°C, 4°C with and without fixation. Internalization is assessed by flow cytometry. In addition, these assays will allow determination of the shedding or production of soluble 35-L1⁺ to L5⁺ protein from the cell surface.
 - (b) The effects of crosslinking the 35-L1⁺ to L5⁺ mAb on growth kinetics, cell cycle disruption or apoptosis will also be assayed on leukemic cell lines and AML samples. Apoptosis is assessed by Annexin V staining or expression of the bcl-2 molecule by cells in culture.
 - (c) Complement dependent cytotoxicity of 35-L1⁺ to L5⁺ targets using anti-35-L1⁺ to L5⁺ mAb and complement is assayed. Targets to be used for this analysis depend on the results of AIM 2. The ability of the mAb to lyse tumor cells *via* antibody dependent cell mediated cytotoxicity (ADCC) is also tested using standard assays. Assays for complement dependent cytotoxicity (CDC) and ADCC have been developed for assessing the ability of the CMRF-44 mAb to lyse target cells.

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In a variation of this assay, CMRF-35A or CMRF-35H is crosslinked with 35-LM antibodies.

EXAMPLE 10

In vivo model

A NOD-SCID mouse model is developed to conduct *in vivo* assays on AML. Such a model provides valuable information of the *in vivo* effects of antagonists and agonists of 35-L1 to L5 (e.g. 35-L1 to L5 mAbs).

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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 <213> homosapiens

<400> 4

Met Trp Leu Pro Trp Ala Leu Leu Leu Leu Trp Val Pro Gly Cys Phe
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Ala Leu Ser Lys Cys Arg Thr Val Ala Gly Pro Trp Gly Ser Leu Ser
 20 25 30

Val Gln Cys Pro Tyr Glu Lys Glu His Arg Thr Leu Asn Lys Tyr Trp
 35 40 45

Cys Arg Pro Pro Gln Ile Phe Leu Cys Asp Lys Ile Val Glu Thr Lys
 50 55 60

Gly Ser Ala Gly Lys Arg Asn Gly Arg Val Ser Ile Arg Asp Ser Pro
 65 70 75 80

Ala Asn Leu Ser Phe Thr Val Thr Leu Glu Asn Leu Thr Glu Glu Asp
 85 90 95

Ala Gly Thr Tyr Trp Cys Gly Val Asp Thr Pro Trp Leu Arg Asp Phe
 100 105 110

His Asp Pro Val Val Glu Val Glu Val Ser Val Phe Pro Ala Ser Thr
 115 120 125

Ser Met Thr Pro Ala Ser Ile Thr Ala Ala Lys Thr Ser Thr Ile Thr
 130 135 140

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Thr Ala Phe Pro Pro Val Ser Ser Thr Thr Leu Phe Ala Val Gly Ala
145 150 155 160

Thr His Ser Ala Ser Ile Gln Glu Glu Thr Glu Glu Val Val Asn Ser
165 170 175

Gln Leu Pro Leu Leu Leu Ser Leu Leu Ala Leu Leu Leu Leu Leu Leu
180 185 190

Val Gly Ala Ser Leu Leu Ala Trp Arg Met Phe Gln Lys Trp Ile Lys
195 200 205

Trp Ile Lys Ala Gly Asp His Ser Glu Leu Ser Gln Asn Pro Lys Gln
210 215 220

Ala Ala Thr Gln Ser Glu Leu His Tyr Ala Asn Leu Glu Leu Leu Met
225 230 235 240

Trp Pro Leu Gln Glu Lys Pro Ala Pro Pro Arg Glu Val Glu Val Glu
245 250 255

Tyr Ser Thr Val Ala Ser Pro Arg Glu Glu Leu His Tyr Ala Ser Val
260 265 270

Val Phe Asp Ser Asn Thr Asn Arg Ile Ala Ala Gln Arg Pro Arg Glu
275 280 285

Glu Glu Pro Asp Ser Asp Tyr Ser Val Ile Arg Lys Thr
290 295 300

<210> 5
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<212> DNA
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acaagggata taacaagtac tgggtgccgag gacagtacga cacgtcatgt gagagcattg 240
tgagagaccaa gggagaagag aaggtggaga ggaatggccg cgtgtccatc agagaccacc 300
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- 55 -

actggtgcaa aattcagaca gtgtgggtcc tggattcatg gtcacgcgat ccctcggacc 420
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 cacctcccat cttcctgggtg gtgaaccctg ggcgaaacct cagcaccagg gaggtgttga 540
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 ctcttggaag atag 674

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 <211> 205
 <212> PRT
 <213> homosapiens
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Ser Leu Lys Gly Pro Gly Ser Val Thr Gly Thr Ala Gly Asp Ser Leu
 20 25 30

Thr Val Trp Cys Gln Tyr Glu Ser Met Tyr Lys Gly Tyr Asn Lys Tyr
 35 40 45

Trp Cys Arg Gly Gln Tyr Asp Thr Ser Cys Glu Ser Ile Val Glu Thr
 50 55 60

Lys Gly Glu Glu Lys Val Glu Arg Asn Gly Arg Val Ser Ile Arg Asp
 65 70 75 80

His Pro Glu Ala Leu Ala Phe Thr Val Thr Met Gln Asn Leu Asn Glu
 85 90 95

Asp Asp Ala Gly Ser Tyr Trp Cys Lys Ile Gln Thr Val Trp Val Leu
 100 105 110

Asp Ser Trp Ser Arg Asp Pro Ser Asp Leu Val Arg Val Tyr Val Ser
 115 120 125

Pro Ala Ile Thr Thr Pro Arg Arg Thr Thr His Pro Ala Thr Pro Pro
 130 135 140

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Ile Phe Leu Val Val Asn Pro Gly Arg Asn Leu Ser Thr Arg Glu Val
145 150 155 160

Leu Thr Gln Asn Ser Gly Phe Arg Leu Ser Ser Pro His Phe Leu Leu
165 170 175

Val Val Leu Leu Lys Leu Pro Leu Leu Leu Ser Met Leu Gly Ala Val
180 185 190

Phe Trp Val Asn Arg Pro Gln Trp Ala Pro Pro Gly Arg
195 200 205

<210> 7
<211> 510
<212> DNA
<213> homosapiens

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gatgctgaca gttattgggtg tgggactgag agacctggaa ttgatcttgg ggtcaaagtt 360
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ccctgccagt gccttcttgg aacttcttta 510

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<211> 174
<212> PRT
<213> homosapiens

<400> 8

Met Trp Leu Ser Pro Ala Leu Leu Leu Leu Ile Leu Pro Gly Tyr Ser
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Ile Ala Ala Lys Ile Thr Gly Pro Thr Thr Val Asn Gly Ser Glu Gln
20 25 30

Gly Ser Glu Gln Gly Ser Leu Thr Val Gln Cys Ala Tyr Gly Ser Gly

- 57 -

35

40

45

Trp Glu Thr Tyr Leu Lys Trp Arg Cys Gln Gly Ala Asp Trp Asn Tyr
50 55 60

Cys Asn Ile Leu Val Lys Thr Asn Gly Ser Glu Gln Glu Val Lys Lys
65 70 75 80

Asn Arg Val Ser Ile Arg Asp Asn Gln Lys Asn His Val Phe Thr Val
85 90 95

Thr Met Glu Asn Leu Lys Arg Asp Asp Ala Asp Ser Tyr Trp Cys Gly
100 105 110

Thr Glu Arg Pro Gly Ile Asp Leu Gly Val Lys Val Gln Val Thr Ile
115 120 125

Asn Pro Ala Gln Cys Leu Ser Leu Leu Pro Thr Asp Asp Arg Val Met
130 135 140

Val Pro Val Ser Ala His Arg Pro Lys Gly Pro Pro Ser Leu Val Thr
145 150 155 160

Arg Asp Pro Asn Pro Cys Gln Cys Leu Leu Gly Thr Ser Leu
165 170

<210> 9
<211> 1026
<212> DNA
<213> homosapiens

<400> 9
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ccgtgacctt ggagaacctc acggcagacg atgcaggaaa ataccgatgt gggattgcaa 480

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aaaaag 1026

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<210> 10
<211> 193
<212> PRT
<213> homosapiens

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<400> 10

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Met Leu Pro Ser Ala Leu Leu Leu Leu Cys Val Pro Gly Cys Leu Thr
1 5 10 15

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Val Ser Gly Pro Ser Thr Val Met Gly Ala Val Gly Glu Ser Leu Ser
20 25 30

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Val Gln Cys Arg Tyr Glu Asp Lys Tyr Lys Thr Phe Asn Lys Tyr Trp
35 40 45

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Cys Arg Gln Pro Cys Leu Pro Ile Trp His Glu Met Val Glu Thr Gly
50 55 60

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```

Gly Ser Glu Gly Val Val Arg Ser Asp Gln Val Ile Ile Thr Asp His
65 70 75 80

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Pro Gly Asp Leu Thr Phe Thr Val Thr Leu Glu Asn Leu Thr Ala Asp
85 90 95

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Asp Ala Gly Lys Tyr Arg Cys Gly Ile Ala Thr Ile Leu Gln Glu Asp
100 105 110

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Gly Leu Ser Gly Phe Leu Pro Asp Pro Phe Phe Gln Val Gln Val Leu

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115	120	125
Val Ser Ser Ala Ser Ser Thr Glu Asn Ser Val Lys Thr Pro Ala Ser		
130	135	140
Pro Thr Arg Pro Ser Gln Cys Gln Gly Ser Leu Pro Ser Ser Thr Cys		
145	150	155 160
Phe Leu Leu Leu Pro Leu Leu Lys Val Pro Leu Leu Leu Ser Ile Leu		
165	170	175
Gly Ala Ile Leu Trp Val Asn Arg Pro Trp Arg Thr Pro Trp Thr Glu		
180	185	190

Ser

<210> 11
 <211> 1352
 <212> DNA
 <213> homosapiens

<400> 11

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tggctgcccc ctgctctgct ccttctcagc ctctcagggt gtttctccat ccaaggccca	180
gagtctgtga gagccccaga gcaggggtcc ctgacgggtc aatgccacta taagcaagga	240
tgggagacct acattaagtg gtggtgccga ggggtgcgct gggatacatg caagatctc	300
attgaaacca gagggtcgga gcaaggagag aagagtgacc gtgtgtccat caaggacaat	360
cagaaagacc gcacgttcac tgtgaccatg gaggggctca ggcgagatga cgcagatggt	420
tactggtgtg ggattgaaag aagaggacct gaccttggga ctcaagtga agtgatcggt	480
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ccaggggaac agcctatcta catgaacttc tccgaacctc tgactaaaga catggccact	720
tagagagatg gatctgcaga gccttcctgc cctggccacg tttccagaag agactcgggc	780
tgtggaagga acatctacga gtccctcggga tgcagtgact gagatagggg ccctgggcct	840

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 <211> 201
 <212> PRT
 <213> homosapiens

<400> 12

Met Trp Leu Pro Pro Ala Leu Leu Leu Leu Ser Leu Ser Gly Cys Phe
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Ser Ile Gln Gly Pro Glu Ser Val Arg Ala Pro Glu Gln Gly Ser Leu
 20 25 30

Thr Val Gln Cys His Tyr Lys Gln Gly Trp Glu Thr Tyr Ile Lys Trp
 35 40 45

Trp Cys Arg Gly Val Arg Trp Asp Thr Cys Lys Ile Leu Ile Glu Thr
 50 55 60

Arg Gly Ser Glu Gln Gly Glu Lys Ser Asp Arg Val Ser Ile Lys Asp
 65 70 75 80

Asn Gln Lys Asp Arg Thr Phe Thr Val Thr Met Glu Gly Leu Arg Arg
 85 90 95

Asp Asp Ala Asp Val Tyr Trp Cys Gly Ile Glu Arg Arg Gly Pro Asp
 100 105 110

Leu Gly Thr Gln Val Lys Val Ile Val Asp Pro Glu Gly Ala Ala Ser
 115 120 125

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Thr Thr Ala Ser Ser Pro Thr Asn Ser Asn Met Ala Val Phe Ile Gly
130 135 140

Ser His Lys Arg Asn His Tyr Met Leu Leu Val Phe Val Lys Val Pro
145 150 155 160

Ile Leu Leu Ile Leu Val Thr Ala Ile Leu Trp Leu Lys Gly Ser Gln
165 170 175

Arg Val Pro Glu Glu Pro Gly Glu Gln Pro Ile Tyr Met Asn Phe Ser
180 185 190

Glu Pro Leu Thr Lys Asp Met Ala Thr
195 200

<210> 13
<211> 812
<212> DNA
<213> homosapiens

<400> 13
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caacagtga tggcttggag cggggctcct tgaccgtgca gtgtgtttac agatcaggct 240
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aaggtagag gacotgggta ctgcagcccc tggagggcga cctctgctat gcagacctga 720
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<210> 14

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<211> 287
 <212> PRT
 <213> homosapiens
 <400> 14

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Ser	Ile	Val	Thr	Gln	Ile	Thr	Gly	Pro	Thr	Thr	Val	Asn	Gly	Leu	Glu
			20					25					30		
Arg	Gly	Ser	Leu	Thr	Val	Gln	Cys	Val	Tyr	Arg	Ser	Gly	Trp	Glu	Thr
		35					40					45			
Tyr	Leu	Lys	Trp	Trp	Cys	Arg	Gly	Ala	Ile	Trp	Arg	Asp	Cys	Lys	Ile
	50					55					60				
Leu	Val	Lys	Thr	Ser	Gly	Ser	Glu	Gln	Glu	Val	Lys	Arg	Asp	Arg	Val
65					70					75					80
Ser	Ile	Lys	Asp	Asn	Gln	Lys	Asn	Arg	Thr	Phe	Thr	Val	Thr	Met	Glu
				85					90					95	
Asp	Leu	Met	Lys	Thr	Asp	Ala	Asp	Thr	Tyr	Trp	Cys	Gly	Ile	Glu	Lys
			100					105					110		
Thr	Gly	Asn	Asp	Leu	Gly	Val	Thr	Val	Gln	Val	Thr	Ile	Asp	Pro	Ala
		115					120					125			
Pro	Val	Thr	Gln	Glu	Glu	Thr	Ser	Ser	Ser	Pro	Thr	Leu	Thr	Gly	His
	130					135					140				
His	Leu	Asp	Asn	Arg	His	Lys	Leu	Leu	Lys	Leu	Ser	Val	Leu	Leu	Pro
145					150					155					160
Leu	Ile	Phe	Thr	Ile	Leu	Leu	Leu	Leu	Leu	Val	Ala	Ala	Ser	Leu	Leu
				165					170					175	
Ala	Trp	Arg	Met	Met	Lys	Tyr	Gln	Gln	Lys	Gly	Glu	Arg	Thr	Trp	Val
			180					185					190		
Leu	Gln	Pro	Leu	Glu	Gly	Asp	Leu	Cys	Tyr	Ala	Asp	Leu	Thr	Leu	Gln
		195					200					205			

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Leu Ala Gly Thr Ser Pro Gln Lys Ala Thr Thr Lys Leu Ser Ser Ala
210 215 220

Gln Val Asp Gln Val Glu Val Glu Tyr Val Thr Met Ala Ser Leu Pro
225 230 235 240

Lys Glu Asp Ile Ser Tyr Ala Ser Leu Thr Leu Gly Ala Glu Asp Gln
245 250 255

Glu Pro Thr Tyr Cys Asn Met Gly His Leu Ser Ser His Leu Pro Gly
260 265 270

Arg Gly Pro Glu Glu Pro Thr Glu Tyr Ser Thr Ile Ser Arg Pro
275 280 285

<210> 15
<211> 2389
<212> DNA
<213> homosapiens

<400> 15
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<210> 16
<211> 287
<212> PRT
<213> homosapiens
<400> 16

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Met	Arg	Pro	Leu	Val	Leu	Leu	Trp	Gly	Cys	Leu	Val	Leu	Pro	Gly	Tyr	1	5	10	15
Glu	Ala	Leu	Lys	Gly	Pro	Lys	Glu	Ile	Ser	Gly	Phe	Glu	Gly	Asp	Thr	20	25	30	
Val	Ser	Leu	Arg	Cys	Thr	Tyr	Val	Glu	Lys	Met	Lys	Glu	His	Arg	Lys	35	40	45	
Tyr	Trp	Cys	Arg	Gln	Gly	Gly	Ile	Leu	Val	Ser	Arg	Cys	Gly	Asp	Ile	50	55	60	
Val	Tyr	Ala	Asn	Gln	Asp	Gln	Glu	Val	Thr	Arg	Gly	Arg	Met	Ser	Ile	65	70	75	80
Arg	Asp	Ser	Pro	Gln	Glu	Leu	Ser	Met	Thr	Val	Ile	Met	Arg	Asp	Leu	85	90	95	
Thr	Leu	Lys	Asp	Ser	Gly	Lys	Tyr	Trp	Cys	Gly	Ile	Asp	Arg	Leu	Gly	100	105	110	
Arg	Asp	Glu	Ser	Phe	Glu	Val	Thr	Leu	Ile	Val	Phe	Pro	Gly	Ser	Ser	115	120	125	
Arg	Pro	Val	Val	Trp	Leu	Pro	Leu	Thr	Thr	Pro	Gln	Asp	Ser	Arg	Ala	130	135	140	
Val	Ala	Ser	Ser	Val	Ser	Lys	Pro	Ser	Val	Ser	Ile	Pro	Met	Val	Arg	145	150	155	160
Met	Met	Ala	Pro	Val	Leu	Ile	Leu	Leu	Ser	Leu	Leu	Leu	Ala	Ala	Gly	165	170	175	
Leu	Ile	Ala	Phe	Gly	Ser	His	Met	Leu	Arg	Trp	Arg	Lys	Lys	Ala	Trp	180	185	190	
Leu	Ala	Thr	Glu	Thr	Gln	Lys	Asn	Glu	Lys	Val	Tyr	Leu	Glu	Thr	Ser	195	200	205	
Leu	Pro	Gly	Asn	Gly	Trp	Thr	Thr	Glu	Asp	Ser	Thr	Ile	Asp	Leu	Ala	210	215	220	

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Val Thr Pro Glu Cys Leu Arg Asn Leu Asn Pro Ser Ala Val Pro Ser
225 230 235 240

Pro Glu Thr Gln Asn Leu Ser Gln Ser Thr Glu Glu Glu Glu Ala Ala
245 250 255

Arg Ser Leu Asp Asp Asp Lys Glu Asp Val Met Ala Pro Pro Pro Leu
260 265 270

Gln Met Ser Ala Glu Glu Leu Ala Phe Ser Glu Phe Ile Ser Val
275 280 285

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<212> DNA
<213> homosapiens

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- 67 -

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<211> 314
<212> PRT
<213> homosapiens

<400> 18

Met Thr Gln Leu Ala Ser Ala Val Trp Leu Pro Thr Leu Leu Leu Leu
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Leu Leu Leu Phe Trp Leu Pro Gly Cys Val Pro Leu His Gly Pro Ser
20 25 30

Thr Met Thr Gly Ser Val Gly Gln Ser Leu Ser Val Ser Cys Gln Tyr
35 40 45

Glu Glu Lys Phe Lys Thr Lys Asp Lys Tyr Trp Cys Arg Gly Ser Leu
50 55 60

Lys Val Leu Cys Lys Asp Ile Val Lys Thr Ser Ser Ser Glu Glu Ala
65 70 75 80

Arg Ser Gly Arg Val Thr Ile Arg Asp His Pro Asp Asn Leu Thr Phe
85 90 95

Thr Val Thr Tyr Glu Ser Leu Thr Leu Glu Asp Ala Asp Thr Tyr Met
100 105 110

Cys Ala Val Asp Ile Ser Leu Phe Asp Gly Ser Leu Gly Phe Asp Lys
115 120 125

Tyr Phe Lys Ile Glu Leu Ser Val Val Pro Ser Glu Asp Pro Gly Pro
130 135 140

Thr Leu Glu Thr Pro Val Val Ser Thr Ser Leu Pro Thr Lys Gly Pro
145 150 155 160

Ala Leu Gly Ser Asn Thr Glu Asp Arg Arg Glu His Asp Tyr Ser Gln
165 170 175

Gly Leu Arg Leu Pro Ala Leu Leu Ser Val Leu Ala Leu Leu Leu Phe
180 185 190

- 68 -

Leu Leu Val Gly Thr Ser Leu Leu Ala Trp Arg Met Phe Gln Lys Arg
 195 200 205

Leu Val Lys Ala Asp Arg His Pro Glu Leu Ser Gln Asn Leu Arg Gln
 210 215 220

Ala Ser Glu Gln Asn Glu Cys Gln Tyr Val Asn Leu Gln Leu His Thr
 225 230 235 240

Trp Ser Leu Arg Glu Glu Pro Val Leu Pro Ser Gln Val Glu Val Val
 245 250 255

Glu Tyr Ser Thr Leu Ala Leu Pro Gln Glu Glu Leu His Tyr Ser Ser
 260 265 270

Val Ala Phe Asn Ser Gln Arg Gln Asp Ser His Ala Asn Gly Asp Ser
 275 280 285

Leu His Gln Pro Gln Asp Gln Lys Ala Glu Tyr Ser Glu Ile Gln Lys
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Pro Arg Lys Gly Leu Ser Asp Leu Tyr Leu
 305 310

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 agatggcaaa ccaacaagaa gtggtggtgc cggggagcaa gctggagcac ttgcagggtc 180
 ctcatccgat ccaactgggtc agagaaagaa acgaagagcg gccggctgtc catcagggtc 240
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 acttactggt gtggtattga aaagtctgga actgaccgtg ggaccagagt taaagtgaac 360
 gtctacttcg gccatatgca gaccttcttc agttcagcag ccacactgac tcctgagagg 420
 gcagcagaga tgtgggtaaa gataccatgt cgacttctaa tcaacttccc tggcccaactg 480
 tggacggcag tacagacatg gtgtcttctg acttgcagaa gaggacttga agccagtcta 540

- 69 -

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tttaccttcg tgctaacact gactcctcct agttcccagg aagcacacag cacaccgtca      660
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<210> 20
 <211> 236
 <212> PRT
 <213> homosapiens

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Met Trp Leu Ser Pro Ala Leu Leu Leu Leu Ser Phe Pro Gly Cys Leu
1          5          10          15

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Ser Ile Gln Gly Pro Ala Leu Val Arg Gly Pro Glu Gln Gly Ser Val
          20          25          30

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Thr Val Gln Cys Arg Tyr Ser Ser Arg Trp Gln Thr Asn Lys Lys Trp
          35          40          45

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Trp Cys Arg Gly Ala Ser Trp Ser Thr Cys Arg Val Leu Ile Arg Ser
          50          55          60

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```

Thr Gly Ser Glu Lys Glu Thr Lys Ser Gly Arg Leu Ser Ile Arg Asp
65          70          75          80

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Asn Gln Lys Asn His Ser Phe Gln Val Thr Met Glu Met Leu Arg Gln
          85          90          95

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Asn Asp Thr Asp Thr Tyr Trp Cys Gly Ile Glu Lys Phe Gly Thr Asp
          100          105          110

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Arg Gly Thr Arg Val Lys Val Asn Val Tyr Phe Gly His Met Gln Thr
          115          120          125

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Phe Phe Ser Ser Ala Ala Thr Leu Thr Pro Glu Arg Ala Ala Glu Met
          130          135          140

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Trp Val Lys Ile Pro Cys Arg Leu Leu Ile Asn Phe Pro Gly Pro Leu
          145          150          155          160

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Trp Thr Ala Val Gln Thr Trp Cys Leu Leu Thr Cys Arg Arg Gly Leu
          165          170          175

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- 70 -

Glu Ala Ser Leu Val Gly Ala Phe Val Gly Gly Leu Met Gln Val Pro
180 185 190

Ser Cys Ser Leu Ala Val Ala Ile Phe Thr Phe Val Leu Thr Leu Thr
195 200 205

Pro Pro Ser Ser Gln Glu Ala His Ser Thr Pro Ser Ser His Ser Ala
210 215 220

Pro Val Ala Ser Lys Glu Glu Met Asn Arg Leu Phe
225 230 235

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<211> 819
<212> DNA
<213> homopiens

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<212> PRT
<213> homopiens

- 71 -

<400> 22

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20 25 30

Arg Val Gln Cys Gln Tyr Ser Pro Ser Tyr Lys Gly Tyr Met Lys Tyr
35 40 45

Trp Cys Arg Gly Pro His Asp Thr Thr Cys Lys Thr Ile Val Glu Thr
50 55 60

Asp Gly Ser Glu Lys Glu Lys Arg Ser Gly Pro Val Ser Ile Arg Asp
65 70 75 80

His Ala Ala Asn Ser Thr Ile Thr Val Ile Met Glu Asp Leu Ser Glu
85 90 95

Asp Asp Ala Gly Ser Tyr Trp Cys Lys Ile Gln Thr Ser Phe Ile Trp
100 105 110

Asp Ser Trp Ser Arg Asp Pro Ser Val Ser Val Arg Val Asn Val Phe
115 120 125

Pro Val Asn Ser Gly Gln Asn Leu Arg Ile Ser Thr Asn Val Met Phe
130 135 140

Ile Phe Gln Leu Trp Ser Leu Leu Ser Ser Ile Gln Phe Gln Val Leu
145 150 155 160

Val Phe Leu Lys Leu Pro Leu Phe Leu Ser Met Leu Cys Ala Ile Phe
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Trp Val Asn Arg Leu
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<210> 23

<211> 2487

<212> DNA

<213> homosapiens

<400> 23

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aggtccagag gaggtgagcg gtcaggagca gggctccttg acagtgcagt gcagatattc	240
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agcagtacca tggctctgat gtgctgcaca accagactca gactaatccc actcctatag	1260
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<400> 24

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Gln Gly Ser Leu Thr Val Gln Cys Arg Tyr Ser Ser Tyr Trp Lys Gly
 35 40 45

Tyr Lys Lys Tyr Trp Cys Arg Gly Val Pro Gln Arg Ser Cys Asp Ile
 50 55 60

Leu Val Glu Thr Asp Lys Ser Glu Gln Leu Val Lys Lys Asn Arg Val
 65 70 75 80

Ser Ile Arg Asp Asn Gln Arg Asp Phe Ile Phe Thr Val Thr Met Glu
 85 90 95

- 74 -

Asp Leu Arg Met Ser Asp Ala Gly Ile Tyr Trp Cys Gly Ile Thr Lys
100 105 110

Gly Gly Pro Asp Pro Met Phe Lys Val Asn Val Asn Ile Asp Gln Ala
115 120 125

Pro Lys Ser Ser Met Met Thr Thr Thr Ala Thr Val Leu Lys Ser Ile
130 135 140

Gln Pro Ser Ala Glu Asn Thr Gly Lys Glu Gln Val Thr Gln Ser Lys
145 150 155 160

Glu Val Thr Gln Ser Arg Pro His Thr Arg Ser Leu Leu Ser Ser Ile
165 170 175

Tyr Phe Leu Leu Met Val Phe Val Glu Leu Pro Leu Leu Leu Ser Met
180 185 190

Leu Ser Ala Val Leu Trp Val Thr Arg Pro Gln Arg Cys Phe Gly Arg
195 200 205

Gly Glu Asn Asp Leu Val Lys Thr His Ser Pro Val Ala
210 215 220

<210> 25
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<212> DNA
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tgagaagatg catttgtcat tgctggtccc ctttctcttc tggatcacag gctgctgcac 180
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tctgaggatg agcgatgctg gcatttactg gtgtggaatt acgaaagtgc caaccatgcc 480
ccccatcacc tccaccacca ccatcttcac agtgacaacc acagtaaaag agaccagcat 540

- 75 -

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tgcagtcctg ttgcttctcc tgttggtggc ctgctctttt gcttgaggga tggtgaggag 720
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ggagcctact tatggcaata ctggctgccc catcacccat gttcccagga caggccttga 960
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tccccactta tagccaatgt accttgaag gtaccaggca ggctgcttca gggatgctgt 1260
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 <211> 296
 <212> PRT
 <213> homosapiens

<400> 26

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 20 25 30

Glu Gln Gly Ser Leu Thr Val Gln Cys Arg Tyr Thr Ser Gly Trp Lys
 35 40 45

Asp Tyr Lys Lys Tyr Trp Cys Gln Gly Val Pro Gln Arg Ser Cys Lys
 50 55 60

Thr Leu Val Glu Thr Asp Ala Ser Glu Gln Leu Val Lys Lys Asn Arg
 65 70 75 80

Val Ser Ile Arg Asp Asn Gln Arg Asp Phe Ile Phe Thr Val Thr Met
 85 90 95

- 76 -

Glu Asp Leu Arg Met Ser Asp Ala Gly Ile Tyr Trp Cys Gly Ile Thr
100 105 110

Lys Val Pro Thr Met Pro Pro Ile Thr Ser Thr Thr Thr Ile Phe Thr
115 120 125

Val Thr Thr Thr Val Lys Glu Thr Ser Met Phe Pro Thr Leu Thr Ser
130 135 140

Tyr Tyr Ser Asp Asn Gly His Gly Gly Gly Asp Ser Gly Gly Gly Glu
145 150 155 160

Asp Gly Val Gly Asp Gly Phe Leu Asp Leu Ser Val Leu Leu Pro Val
165 170 175

Ile Ser Ala Val Leu Leu Leu Leu Leu Leu Val Ala Ser Leu Phe Ala
180 185 190

Trp Arg Met Val Arg Arg Gln Lys Lys Asp Leu Ser Leu Lys Gln Pro
195 200 205

Arg Thr Ser Pro Gly Ser Ser Trp Lys Lys Gly Ser Ser Met Ser Ser
210 215 220

Ser Gly Lys Asp His Gln Glu Glu Val Glu Tyr Val Thr Met Ala Pro
225 230 235 240

Phe Pro Arg Glu Glu Val Ser Tyr Ala Ala Leu Thr Leu Ala Gly Leu
245 250 255

Gly Gln Glu Pro Thr Tyr Gly Asn Thr Gly Cys Pro Ile Thr His Val
260 265 270

Pro Arg Thr Gly Leu Glu Glu Glu Thr Thr Glu Tyr Ser Ser Ile Arg
275 280 285

Arg Pro Leu Pro Ala Ala Met Pro
290 295

<210> 27
<211> 114
<212> PRT

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<213> homosapiens

<400> 27

Gly Cys Cys Thr Ala Gln Asp Pro Val Thr Gly Pro Glu Glu Val Ser
1 5 10 15

Gly Gln Glu Gln Gly Ser Leu Thr Val Gln Cys Arg Tyr Asp Ser Gly
20 25 30

Trp Lys Asp Tyr Lys Lys Tyr Trp Cys Arg Gly Ala Tyr Trp Lys Ser
35 40 45

Cys Glu Ile Leu Val Glu Thr Asp Ala Ser Glu Gln Leu Val Lys Glu
50 55 60

Asn Arg Val Ser Ile Arg Asp Asp Gln Thr Asp Phe Ile Phe Thr Val
65 70 75 80

Thr Met Glu Asp Leu Arg Met Ser Asp Ala Asp Ile Tyr Trp Cys Gly
85 90 95

Ile Thr Lys Ala Gly Thr Asp Pro Met Phe Lys Val Asn Val Asn Ile
100 105 110

Asp Pro

DATED this twenty-ninth day of November 2002.

The Corporation of the Trustees of the Order of the Sisters of Mercy in Queensland
by DAVIES COLLISION CAVE
Patent Attorneys for the Applicant

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PileUp of: @/home/mmri00/Georgina/.WAG/pileup-26532.26547

Symbol comparison table: GenRunData:pileupdna.cmp CompCheck: 6876

GapWeight: 5.000

GapLengthWeight: 0.300

pileup.msf MSF: 1841 Type: N September 4, 19102 09:13 Check: 8239 ..

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35-L2 ..... [SEQ ID NO:7]
35-L5 ..... [SEQ ID NO:13]
35-L4 ..... [SEQ ID NO:11]
35-L3 ..... [SEQ ID NO:9]
35A CTCTAAAGGC CACTAGCACC CATCCAGAG CTGTCAGCAC CGGCCTCAGC [SEQ ID NO:1]
35-L1 ..... [SEQ ID NO:5]
35H ..... [SEQ ID NO:3]
35-L7 (AW8) ..... [SEQ ID NO:9]

51
35-L2 .....
35-L5 .....
35-L4 .....
35-L3 .....
35A CCAGGGGGCT CTCCTCCCTGA GCTTCCTGTA GCCCTGACCC TCTCCAGCCT
35-L1 .....
35H .....
35-L7 (AW8) .....
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Figure 1

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101	150	
35-L2	[SEQ ID NO:7]	
35-L5	[SEQ ID NO:13]	
35-L4	[SEQ ID NO:11]	
35-L3	[SEQ ID NO:9]	
35A	[SEQ ID NO:1]	
35-L1	[SEQ ID NO:5]	
35H	[SEQ ID NO:3]	
35-L7 (AW8)	[SEQ ID NO:9]	
151	200	
35-L2		
35-L5		
35-L4		
35-L3		
35A		
35-L1		
35H		
35-L7 (AW8)		
201	250	
35-L2		
35-L5		
35-L4		
35-L3		
35A		
35-L1		
35H		
35-L7 (AW8)		

Figure 1 (continued)

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251          .ATGTGGCTG TCCCCAGCTC TGCTGCTTCT CATCTCCCA [SEQ ID NO:7]
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35-L5 AAGGCAGAGC CATGTGGCTG CCCCCTGCTC TGCTCCTTCT CAGCCTCTCA [SEQ ID NO:11]
35-L4 G.GCTGGGGC TGCCATGCTG CCTTCAGCTC TGCTCCTTCT CTGTGTCCCA [SEQ ID NO:9]
35A   G.GCCTGGGC CTCGTGGCGG TCTTCAGCTC TGCTCCTCCT GCTTGTCCCA [SEQ ID NO:1]
35-L1 GAGACAGGAA CATGTGGCTG CTCCCAGCTC TACTCCTTCT CTGCCCTCTCA [SEQ ID NO:5]
35H   . . . . . GG AGGAGCTGGG ACTCTGGCTT GTGTTTTCCA [SEQ ID NO:3]
35-L7 (AW8) TATATATTGT AGAAGATAGT CTGACCAATGC TGCCCAGGCT GCTCTCAAAC [SEQ ID NO:9]

301
35-L2 GGTACTCCA TTGCCGCTAA AATCACTGGT CCAACAACAG TGAATGGCTC
35-L5 GGCTACTCCA TTGTCACTCA AATCACCGGT CCAACAACAG TGAATGGCTT
35-L4 GGCTGTTTC. . . . . TC CATCCAAGGC CCAGAGTCTG TGAGAGCCCC
35-L3 GGCTGTCTGA CTG. . . . . TGAGTGGC CCCAGCACCG TGATGGGCGC
35A   GGCTATTTC CTC. . . . . TGAGCCAC CCCATGACCG TGGCGGGCCC
35-L1 GGCTGTTTGT CTC. . . . . TGAAGGGC CCCGGCTCTG TGA CTGGCAC
35H   GGATGTTTGT CTC. . . . . TGAGCAAA TGCAGGACCG TGGCGGGCCC
35-L7 (AW8) TCCTGGACTC AAGTGATCCA CCTGCCTTGG CCTCTAAAG TGCTGGGATT

351
35-L2 GGAGCAGGGC TCATTGACTG TGCAGTGTGC TTATGGCTCA GGCTGGGAGA
35-L5 GGAGCGGGGC TCCTTGACCG TGCAGTGTGT TTACAGATCA GGCTGGGAGA
35-L4 AGAGCAGGGG TCCCTGACCG TTCAATGCCA CTATAAGCAA GGATGGGAGA
35-L3 CGTGGGGGAA TCCCTGAGTG TGCAGTGTGC GTATGAAGAC AAATACAAGA
35A   CGTGGGGGGA TCCCTGAGTG TGCAGTGTGC CTATGAGAAG GAACACAGGA
35-L1 TGCGGGGGAC TCTCTGACAG TGTGGTGTCA GTATGAGAGC ATGTACAAGG
35H   CGTGGGGGGA TCCCTGAGTG TGCAGTGTCC CTATGAGAAG GAACACAGGA
35-L7 (AW8) GCAGGGGTAA GCCACCGCAC CCGGCTTACA TTTTTTTTAA ACTTTTAAAA

```

Figure 1 (continued)

401 CCTACTTGAA GTGGCGGTGT CAAGGAGCTG ATTGGAATTA CTGTAACATC [SEQ ID NO:7]
 35-L2 CCTACTTGAA GTGGTGTGT GTGGAGCTA TTGGCGTGA CTGCAAGATC [SEQ ID NO:13]
 35-L5 CCTACATTAA GTGGTGTGT CGAGGGGTGC GCTGGGATAC ATGCAAGATC [SEQ ID NO:11]
 35-L4 CGTTTAACAA ATACTGGTGC AGACAACCAT GCTTGCCAAT TTGGCATGAA [SEQ ID NO:9]
 35-L3 CCCTCAACAA ATTCTGGTGC AGACCACCAC AGATTCTCCG ATGTGACAAG [SEQ ID NO:1]
 35A GATATAACAA GTACTGGTGC CGAGGACAGT ACGACACGTC ATGTGAGAGC [SEQ ID NO:5]
 35-L1 CCCTCAACAA ATACTGGTGC AGACCACCAC AGATTTTCCT ATGTGACAAG [SEQ ID NO:3]
 35H AGTATCCGGT GATAAGATGG AAAGAAATAT GAGGTCAGG GTCAGAAGTC [SEQ ID NO:9]
 35-L7 (AW8)

450
 451 CTTGTGTTAAA CAAATGGATC AGAGCAGGAG GTAAAGAAGA ATCGAGTTTC
 35-L2 CTTGTGTTAAA CCAAGTGGTC AGAGCAGGAG GTGAAGAGGG ACCGGGTGTC
 35-L5 CTCATTGAAA CCAAGAGGTC GGAGCAAGGA GAGAAGAGTG ACCGTGTGTC
 35-L4 ATGGTGGAGA CCGGAGGTC TGAGGAGTG GTGAGGAGTG ACCAAGTGAT
 35-L3 ATTGTGGAGA CCAAGGGTC AG...CAGGG AAAAGGAATG GCCGAGTGTC
 35A ATTGTGGAGA CCAAGGGAGA AGAGAAGTG GAGAGGAATG GCCGCGTGTC
 35-L1 ATTGTGGAGA CCAAGGGTC AG...CAGGA AAAAGGAACG GCCGAGTGTC
 35H CTTTGTGCAG TCAGAGGGGC TGTGTCTCTG GACAGG...G TTCCAATGGG
 35-L7 (AW8)

500
 501 CATCAGGGAC AATCAGAAAA ACCACGTGTT CACCGTGACC ATGGAGAATC
 35-L2 CATCAAGGAC AATCAGAAAA ACCGCACGTT CACTGTGACC ATGGAGGATC
 35-L5 CATCAAGGAC AATCAGAAAG ACCGCACGTT CACTGTGACC ATGGAGGGGC
 35-L4 CATCAGGGAC CATCCTGGAG ACCTCACCTT CACCGTGACC TTGGAGAACC
 35-L3 CATCAGGGAC AGTCCCTGCA AACTCAGCTT CACAGTGACC CTGGAGAATC
 35A CATCAGGGAC CACCCGGAGG CTCTCGCCTT CACTGTGACC ATGCAGAAC
 35-L1 CATCAGGGAC AGTCCCTGCA AACTCAGCTT CACAGTGACC CTGGAGAATC
 35H CAT.GGGGAG TTGCAAGTTC TCCTGTTTAT GACTCTGTCC AAGGAGTCCT
 35-L7 (AW8)

Figure 1 (continued)

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551      600
35-L2    TCATAAGAGA TGATGCTGAC AGTTATTGGT GTGGGACTGA GAGACCT... [SEQ ID NO:7]
35-L5    TCATGAAAC  TGATGCTGAC ACTTACTGGT GTGGAATTGA GAAAACT... [SEQ ID NO:13]
35-L4    TCAGGCAGGA TGACGCAGAT GTTTACTGGT GTGGGATTGA AAGAAGA... [SEQ ID NO:11]
35-L3    TCACGGCAGA CGATGCAGGA AAATACCGAT GTGGGATTGC AACATACTG [SEQ ID NO:9]
35A      TCACAGAGGA GGACGCAGGC ACCTACTGGT GTGGGGTGGG TACACCGTGG [SEQ ID NO:1]
35-L1    TCAATGAAGA TGATGCTGGA TCTTACTGGT GCAAAATTCA GACAGTGTGG [SEQ ID NO:5]
35H      TCACAGAGGA GGATGCAGGC ACCTACTGGT GTGGGGTGGG TACACCGTGG [SEQ ID NO:3]
35-L7 (AW8) CCAAGGCCTG TTCACCCAGA GGATAGCACC GAGTATGCTC AGGAGCAGAG [SEQ ID NO:9]

601      650
35-L2    ...GGAATTG ATCTTGGGGT CAAAGTTCAA GTGACCATTG ACCCAGC.TC
35-L5    ...GGAAATG ACCTTGGGGT CACAGTTCAA GTGACCATTG ACCCAGCACC
35-L4    ...GGACCTG ACCTTGGGAC TCAAAGTGAA GTGATCGTTG ACCCAGAGGG
35-L3    CAGGAAGATG GCCTGTCTGG TTTCTGCCC GATCCCTTCT TCCAGGTTCA
35A      CTCCGAGACT TTCATGATCC CATTGTCGAG GTTGAGGTGT CCGTGTTCCT
35-L1    GTCTGTGGAT CATGGTCACG CGATCCCTCG GACCTGGTTA GGTGTATGT
35H      CTCCGAGACT TTCATGATCC CGTTGTCGAG GTTGAGGTGT CCGTGTTCCT
35-L7 (AW8) GCACCTTCAG GAGTGGCAGA AG.....

651      700
35-L2    AGTGCCTGAG TCTGTTGCCC ACAGATGAC. .AGGTGATG GTTCCAGTTT
35-L5    AGTCACCCAA GAAGAACTA GCAGCTCCCC AACTCTGACC GGCCACCACT
35-L4    AGCGGCTTCC ACAACAGCA GCTCACCTAC CAACAGCAAT ATGGCAGTGT
35-L3    AGTGTGGTC TCATCGGCTT CCACTACTGA GAACTCTGTG AAGACACCTG
35A      GGCCGGGACG ACCACAGCCT CCAGCCCCCA GAGCTCCATG GGCACCTCAG
35-L1    TTCCCCAGCA ATTACAACCC CAAG..... GAGGACCACA CATCCAGCCA
35H      GGCATCAACG TCAATGACAC CTGCAAGTAT CACTGCGGCC AAGACCTCAA
35-L7 (AW8) .....

```

Figure 1 (continued)

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35-L2      701      CAGCCACAG  GCCAA.....GGGACCCC  CTTCCCTGGT  AACCAAGAG  [SEQ ID NO:7]
35-L5      TGGACAACAG  GCACAAGCTC  CTGAAGCTCA  GTGTCTCTCT  GCCCTTCATC  [SEQ ID NO:13]
35-L4      TCATCGGCTC  CCACAAGAGG  AACCACTACA  TGCTCCTGGT  ATTGTGAAG  [SEQ ID NO:11]
35-L3      CATCTCCAC  CAGGC.....GTGCACACCT  GGCCAGCGT  GACCAGAAAG  [SEQ ID NO:9]
35A      GTCCTCCAC  GAAGCTGCC  GTGCACACCT  GGCCAGCGT  GACCAGAAAG  [SEQ ID NO:1]
35-L1      CACTCCCAT  CTTCTGGTG  GTGAACCTTG  GGCGAAACCT  CAGCACCAGG  [SEQ ID NO:5]
35H      CA.ATCAAA  CTGCATTTC  ACCTGTATCA  TCCACTACCC  TGTTCGAGT  [SEQ ID NO:3]
35-L7 (AW8) .....  [SEQ ID NO:9]

35-L2      751      CCCAATCCCT  GCCAGTGCCT  TCTTGGA...CTTCT  TTA.....
35-L5      TTCACCATAT  TGCTGTGCT  TTTGGTGG...CCGCC  TCACTCTTGG
35-L4      GTGCCCATCT  TGCTCATCT  GGTCACTG...CCATC  CTCGTGGTTGA
35-L3      .....CCAGCCA  ATGCCAAGG...G  TCCCTGCCCA
35A      GACAGCCCG  AACCCAGCC  ACACCTGG...C  TCCCTGTTCA
35-L1      GA.....GG  TGTGACCCA  AAATTCAGG...G  TTCCGGCTCA
35H      GGGTGCCACC  CACAGTGCCA  GCATCCAGGA  GGAACTGAG  GAGTGGTGA
35-L7 (AW8) .....

35-L2      801      CTTGGAGGAT  GATGAAGTAC  CAGCAGAAAG  GTGAGAGGAC  CTGGGTACTG
35-L5      AGGGTCTCA  GAGGTCCCT  GAGGAGCCAG  GGAACAGCC  TATCTACATG
35-L4      GCAGCACCTG  CTTCTGCTT  CTCCCACTCC  TGAAGTGCC  TCTGCTCCTG
35-L3      GCAATGTCCG  CTTCTGCTC  CTGGTCTCT  TGGAGTGCC  CCTGCTCCTG
35A      GCAGCCCTCA  CTTCTGCTC  GTGGTCTTC  TGAAGTGCC  CCTGCTCCTG
35H      ACTCACAGCT  CCGCTGCTC  CTCTCCCTGC  TGGCATTTGT  GCTGCTTCTG
35-L7 (AW8) .....

```

Figure 1 (continued)

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851          900
35-L2      ..CAGCCCT GGAGGGGAC CTCTGCTATG CAGACCTGAC CCTGCAGCTG [SEQ ID NO:7]
35-L5      AACTTCTCCG AACCTCTGAC TAAAGACATG GCCACTTAGA GAGATGGATC [SEQ ID NO:13]
35-L4      AGCATACTCG GTGCTATCCT CTGGGTGAAC AGGCCTTGA .. [SEQ ID NO:11]
35-L3      AGCATGCTGG GTGCCGTCCT CTGGGTGAAC AGACCTCAGA .. [SEQ ID NO:9]
35A        AGCATGCTGG GTGCTGTTTT CTGGGTGAAC AGGCCTCAGT .. [SEQ ID NO:1]
35-L1      TTGGTGGGG CCTCCCTGCT AGCCTGGAGG ATGTTTCAGA AATGGATCAA [SEQ ID NO:5]
35H        .. [SEQ ID NO:3]
35-L7 (AW8) .. [SEQ ID NO:9]

901          950
35-L2      GCCGGAACCT CCCGCAAAA GGCTACCACG AAGCTTTCCT CTGCCCAGGT
35-L5      TGCAGAGCCT TCCTGCCCTG GCCACGTTTC CAGAAGAGAC TCGGGCTGTG
35-L4      .....GGACT CCTTGGACAG AGTCATGAAC AGGAGAATT GCAACACCCC
35-L3      .....GAAGC TCTAGAAGCA GGCAGAAATTG GCCCAAGGT GAGAACCAGT
35A        .....GGGT CCTCCTGGAA GATAG.....
35-L1      AGCTGGTGAC CATTGAGAGC TGTCACAGAA CCCCAAGCAG GCTGCCACGC
35H        .. [SEQ ID NO:1]
35-L7 (AW8) .. [SEQ ID NO:1]

951          1000
35-L2      TGACCAGGTG GAAGTGAAT ATGTCACCAT G.....
35-L5      GAAGGAACAT CTACGAGTCC TCGGGATGCA GTGACTGAGA TAGGGGCCCT
35-L4      ATGCCCATTG GAACCCCTGTC CAGAGACACA GCCCTCTGA CTGCAAAAAG
35-L3      AGCATCTGCT GTCCATCAAG GGCCTGTGCT GCAACAGAGC CCCTCT.GGG
35A        .....
35-L1      AGAGTGAGCT GCACTACGCA AATCTGGAGC TGCTGATGTG GCCTCTGCAG
35H        .. [SEQ ID NO:1]
35-L7 (AW8) .. [SEQ ID NO:1]

```

Figure 1 (continued)

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35-L2	1001	1050	[SEQ ID NO:7]
35-L5	[SEQ ID NO:13]
35-L4	GGCCCTCCGC	CCTGGCCTTG	GAGCTGGTG
35-L3	GACTTCTGAC	CCTGACCCCTC	ATATTCTTTT
35A	GACTGGAATG	ACCTCCTGAC	CATCAAGGCC
35-L1
35H	GAAAAGCCAG	CACCACCAAG	GGAGGTGGAG
35-L7 (AW8)
35-L2	1051	1100	[SEQ ID NO:9]
35-L5	[SEQ ID NO:1]
35-L4	GCTCAGGGAC	TTAGCCAGGT	CCTCTCCTGA
35-L3	TTTTTAAAG	TTAAAAAAA	AATGTAGGCC
35A	GGACTGGAAT	GACCTCCTGA	CCACTCCCTC
35-L1
35H	CTCCCCCAGG	GAAGAACCTC	ACTATGCCCTC
35-L7 (AW8)
35-L2	1101	1150	[SEQ ID NO:3]
35-L5	[SEQ ID NO:9]
35-L4	TGCCAGCACC	TGTTCTCTTG	GTCAGGAGCT
35-L3	GCAATCCCAG	CACTTTGGGA	GGCCAAAGCA
35A	TCCTCTGGAA	TCCTTTGTGA	GCCTCCTTCA
35-L1
35H	CCAACAGGAT	AGCTGCTCAG	AGGCCTCGGG
35-L7 (AW8)

Figure 1 (continued)

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1151	1200	
35-L2	[SEQ ID NO:7]
35-L5	[SEQ ID NO:13]
35-L4	CTGGACGACT CTGTCCCCAC TGCTGGAATA ACTCGGGCAC AGAGCATGGG	[SEQ ID NO:11]
35-L3	GGGAAGTTTG AGAGCCCTGG CAGCATGGTC AGACCTCATC TCTACAAAAA	[SEQ ID NO:9]
35A	CCAACATGTG ACACATGAGG ACTTTAGAGC ACAATGGATC	[SEQ ID NO:1]
35-L1	[SEQ ID NO:5]
35H	TACAGTGTGA TAAGGAAGAC ATAGGCTTTT GTCCTGCCTC GCCATCGGAG	[SEQ ID NO:3]
35-L7 (AW8)	[SEQ ID NO:9]
1201	1250	
35-L2	
35-L5	
35-L4	ACCAAGTAC AGAAGAGGT TGGGGGAGAC CCCCCAGCC CTAGACTTCC	
35-L3	AAAAAAAAA G.....	
35A	
35-L1	
35H	CTCTCATGGG CCCAGGAAG TCCAGGGACA GCTCCCTTAT ACCTGGCCCA	
35-L7 (AW8)	
1251	1300	
35-L2	
35-L5	
35-L4	ATCATTCGG AGACCAATC AACACCGTCT TTGCCTGAGA ACCTGATATA	
35-L3	
35A	
35-L1	
35H	CGTCTTCTC AGCCTGCCCT CGACAACAGT GACCAACAGA CAGGCAGCTG	
35-L7 (AW8)	

Figure 1 (continued)

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1301	1350	
35-L2	[SEQ ID NO:7]	
35-L5	[SEQ ID NO:13]	
35-L4	[SEQ ID NO:11]	
35-L3	[SEQ ID NO:9]	
35A	[SEQ ID NO:1]	
35-L1	[SEQ ID NO:5]	
35H	[SEQ ID NO:3]	
35-L7 (AW8)	[SEQ ID NO:9]	
1351	1400	
35-L2		
35-L5		
35-L4		
35-L3		
35A		
35-L1		
35H		
35-L7 (AW8)		
1401	1450	
35-L2		
35-L5		
35-L4		
35-L3		
35A		
35-L1		
35H		
35-L7 (AW8)		

Figure 1 (continued)

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1451	1550
35-L2	[SEQ ID NO:7]
35-L5	[SEQ ID NO:13]
35-L4	[SEQ ID NO:11]
35-L3	[SEQ ID NO:9]
35A	[SEQ ID NO:1]
35-L1	[SEQ ID NO:5]
35H	[SEQ ID NO:3]
35-L7 (AW8)	[SEQ ID NO:9]
1501	1550
35-L2	
35-L5	
35-L4	
35-L3	
35A	
35-L1	
35H	
35-L7 (AW8)	
1551	1600
35-L2	
35-L5	
35-L4	
35-L3	
35A	
35-L1	
35H	
35-L7 (AW8)	

Figure 1 (continued)

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1601	1650	
35-L2	[SEQ ID NO:7]
35-L5	[SEQ ID NO:13]
35-L4	[SEQ ID NO:11]
35-L3	[SEQ ID NO:9]
35A	[SEQ ID NO:1]
35-L1	[SEQ ID NO:5]
35H	AGAGTGCCAA AGCGAGATC TGTTCACTG GGGGCCATGG AGGGGGGACC	[SEQ ID NO:3]
35-L7 (AW8)	[SEQ ID NO:9]
1651	1700	
35-L2	
35-L5	
35-L4	
35-L3	
35A	
35-L1	
35H	CACTAAAGAT CAAGATCAA GATTCTCCCC ATCTCAGACA CAAGGAAACT	
35-L7 (AW8)	
1701	1750	
35-L2	[SEQ ID NO:7]
35-L5	[SEQ ID NO:13]
35-L4	[SEQ ID NO:11]
35-L3	[SEQ ID NO:9]
35A	[SEQ ID NO:1]
35-L1	[SEQ ID NO:5]
35H	GAGGCCAGAG GGAGGAGAGA ATTGCTCATG GCTCCAGAAC TGGTGGCAAG	[SEQ ID NO:3]
35-L7 (AW8)	[SEQ ID NO:9]

Figure 1 (continued)

1751	1800	
35-L2	[SEQ ID NO:7]	
35-L5	[SEQ ID NO:13]	
35-L4	[SEQ ID NO:11]	
35-L3	[SEQ ID NO:9]	
35A	[SEQ ID NO:1]	
35-L1	[SEQ ID NO:5]	
35H	[SEQ ID NO:3]	
35-L7 (AW8)	[SEQ ID NO:9]	
1801	1841	
35-L2		
35-L5		
35-L4		
35-L3		
35A		
35-L1		
35H		
35-L7 (AW8)		

Figure 1 (continued)

PileUp of: @/home/mmri00/Georgina/.WAG/pileup-26028.26030

Symbol comparison table: GenRunData:pileuppep.cmp CompCheck: 1254

GapWeight: 3.000

GapLengthWeight: 0.100

pileup.msf MSF: 336 Type: P September 4, 19102 09:05 Check: 3277 ..

Name: 35-L5	Len: 336	Check: 3658	Weight: 1.00
Name: 35-L2	Len: 336	Check: 8520	Weight: 1.00
Name: 35-L4	Len: 336	Check: 6004	Weight: 1.00
Name: CMRF-35A	Len: 336	Check: 8028	Weight: 1.00
Name: CMRF-35H	Len: 336	Check: 6906	Weight: 1.00
Name: 35-L1	Len: 336	Check: 3613	Weight: 1.00
Name: 35-L3	Len: 336	Check: 6548	Weight: 1.00

//

35-L5MPLL	TLYLILFWLS	GYSIVTQITG	PTTVN.....G	LERGSLTVQC	[SEQ ID NO:14]
35-L2MWL	SPALLLLILP	GYSIAAKITG	PTTVNGSEQG	SEQGSLTVQC	[SEQ ID NO:8]
35-L4MWL	PPALLLLLSL	GCF...SIQG	PESV....RA	PEQGSLTVQC	[SEQ ID NO:12]
CMRF-35A	MTARAWASWR	SSALLLLLLVP	GYF...PLSH	PMTVA....G	PVGGSLSVQC	[SEQ ID NO:2]
CMRF-35HMWL	PWALLLLMVP	GCF...ALSK	CRIVA....G	PW.GSLSVQC	[SEQ ID NO:4]
35-L1MWL	LPALLLLCLS	GCL...SLKG	PGSVT....G	TAGDSLTVWC	[SEQ ID NO:6]
35-L3ML	PSALLLLCVP	GCL...TVSG	PSTVM....G	AVGESLSVQC	[SEQ ID NO:10]

Figure 2

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51 100
 35-L5 VYRSGWETYL KWCRCGAIWR DCKILVKTSG SEQEVKRDV SIKONQKRT [SEQ ID NO:14]
 35-L2 AYSGGWETYL KWRCQGADWN YCNILVKTNG SEQEVKKNRV SIRDNQKNHV [SEQ ID NO:8]
 35-L4 HYKQGWETYL KWWCRCGVRWD TCKILJLIE TRG SEQEKSDDV SIKONQKDR [SEQ ID NO:12]
 CMRF-35A RYEKEHRTLN KWCRCRPPQIL RCDKIVETKG SAG.KRNGRV SIRDSPANLS [SEQ ID NO:2]
 CMRF-35H PYEKEHRTLN KYWCRPPQIF LCDKIVETKG SAG.KRNGRV SIRDSPANLS [SEQ ID NO:4]
 35-L1 QYESMYKGYN KYWCRGQYDT SCESIVETKG EEKVERNGRV SIRDHPEALA [SEQ ID NO:6]
 35-L3 RYEDKYKTFN KYWCRQPCLP IWHMVMETGG SEGVRSDQV IITDHPGDLT [SEQ ID NO:10]

150
 101
 35-L5 FTVTMEDLMK TDADTYWCGI EKT..... ..GNDLGVTV QVTIDPA...
 35-L2 FVTMENLKR DDADSYWCGT ERP..... ..GIDLGVKV QVTINPAQCL
 35-L4 FVTMEGLRR DDADVWCGI ERR..... ..GPDGLGTQV KVIDDPEGAA
 CMRF-35A FVTLENLTE EDAGTYWCGV DTPWLRD... ..FHDPIVEV EVSVFPAGTT
 CMRF-35H FVTLENLTE EDAGTYWCGV DTPWLRD... ..FHDPIVEV EVSVFPAGTT
 35-L1 FVTMQNLNE DDAGSYWCKI QTVWVLDSWS ...RDPSDLV RYVSPAITT
 35-L3 FVTLENLTA DDAGKYRCGI ATILQEDGLS GFELDPFFQV QVLVSSASST

200
 151
 35-L5PVTQE..... ..ETSSSPTLT GHHLNDRHKL
 35-L2 SLLPTDDRV VPVSAH..... ..RPKGPPSLV TRDPNPCQCL
 35-L4 S TTASSP..... ..TNSNMAVFI GSHKRNHYML
 CMRF-35A TASSPQSSMG TSGPPTKLPV ...HTWPSVT RKDSPEPSPH PGSLEFNVRF
 CMRF-35H MTPASITAAK TSTITTAFTP VSSTTLFAVG ATHSASIQEE TEEVNSQLP
 35-L1P RRTTHPATPP IFLVNPGRN LSTREVLTON SGFRLSSPHF
 35-L3E NSVKTASP..... ..TRPSQCQG S..LPSSTCF

Figure 2 (continued)

	201	250
35-L5	LKLSVLLPLI FTILLILLVA ASLLAWRMK YQQKGERTWV LQPLEGDLCY	[SEQ ID NO:14]
35-L2	LGTSL.....	[SEQ ID NO:8]
35-L4	L VFV KVPILLILVT AILWLKGSQR VPPEPGEQPI YMNFEPLTK	[SEQ ID NO:12]
CMRF-35A	LLLVLLLEPL LL...SMLG AVLWVNRPPQR S....SRSR QNWPKGENQ*	[SEQ ID NO:2]
CMRF-35H	LLLSLLALLL LLLVGASLLA WRMFQKWIKW IKAGDHSLS QNPQKAATQS	[SEQ ID NO:4]
35-L1	LLVLLKLPL LL...SMLG AVFWVNRPPQW APPGR*....	[SEQ ID NO:6]
35-L3	LLPLLLKVPL LL...SILG AILWVNRPPWR TPWTES*....	[SEQ ID NO:10]

35-L5	251	ADLTQLAGT	SPQKATTKLS	SAQVDQVEVE	YVTMASLPKE	DISYASLTIG	300
35-L2		
35-L4		DWAT*	
CMRF-35A		
CMRF-35H		ELHYANLELL	MWPLQEKPA	PREVEVEYST	VASPREELHY	ASVWFSNTN	
35-L1		
35-L3		

	301	336
35-L5	AEDQETTCN	RGPEETPEYS
35-L2
35-L4
CMRF-35A-protein
CMRF-35H-protein	RIAAQRPREE	EPDSYDVIR
35-L1
35-L3

Figure 2 (continued)

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Cells	35-L1	35-L2	35-L3	35-L4	35-L5
CD3 T lymphocytes	-	?	-	-	-
CD19 B lymphocytes	-	?	+	+	+
CD15 Granulocytes	-	?	-	-	-
CD16 NK cells	-	?	-	-	-
CD14 Monocytes	+	?	+	+	+
Lin- DC	-	?	+	+	+
CD11c+ Myeloid DC	-	?	ND	ND	-
CD11c- Lymphoid DC	-	?	ND	ND	-
MoDC	-	?	+	+	+
MoDC + LPS	-	?	+	+	+
PBMC	+	?	+	+	+

Figure 3

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	35-L1	35-L2	35-L3	35-L4	35-L5
Jurkat	-	?	-	-	-
HSB	-	?	-	+	-
Molt4	-	?	-	-	-
Daudi	-	?	+	+	+/-
Raji	-	?	+	-	?
Mann	-	?	-/+	+	-
Wt49	-	?	+	+	-
KG1	-	?	-	-	+
Hel	-	?	+	+	+
HL60	-	?	+	+	+

Figure 3(continued)

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	35-L1	35-L2	35-L3	35-L4	35-L5
NB4	-	?	-	-	-
Thp1	-	?	-	-	-
Monomac6	-	?	=	-	-
U937	+	?	+	+	+
K562	-	?	+	-	-
L428	-	?	=	-	-
HDLM-2	-	?	+	-	-
KM-H2	-	?	+	-	-

Figure 3(continued)

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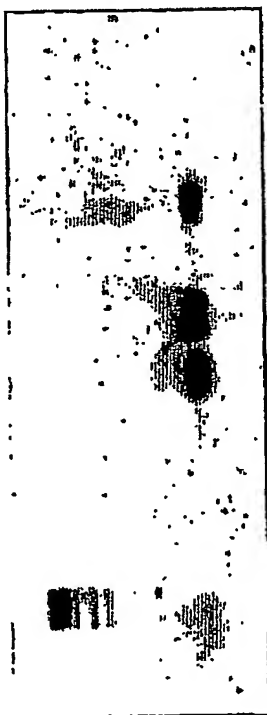


Figure 4

pileUp of: @/home/mmri00/Georgina/.WAG/pileup-16229.16245

Symbol comparison table: GenRunData:pileupdna.cmp CompCheck: 6876

GapWeight: 5.000
GapLengthWeight: 0.300

pileup.msf MSF: 2554 Type: N September 6, 19102 14:32 Check: 8705 ..

Name: m35-hRNA	Len: 2554	Check: 4672	Weight: 1.00
Name: m35ge-RNA	Len: 2554	Check: 5363	Weight: 1.00
Name: m35-dRNA	Len: 2554	Check: 3690	Weight: 1.00
Name: m35-frNA	Len: 2554	Check: 2914	Weight: 1.00
Name: m35-aRNA	Len: 2554	Check: 1598	Weight: 1.00
Name: m35c1RNA	Len: 2554	Check: 468	Weight: 1.00

//

1	50
m35-hRNA GAAGTTAC [SEQ ID NO:23]
m35ge-RNA CCGGAAG TGGCTAAAGG AGGAAGTGCC [SEQ ID NO:25]
m35-dRNA AACACATGGA [SEQ ID NO:19]
m35-frNA	AGGAAGTAGC TCAGAGTGCA AAGGAAGCAG ATAAGAAAAA AACACATGGA [SEQ ID NO:21]
m35-aRNA [SEQ ID NO:15]
m35c1RNA [SEQ ID NO:17]

Figure 5

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	100		
m35-hRNA	51	TGAGAGAAAGT GAACAAGAGA GACCTAAAGG CAACTCAAGC TGAGCTGCCG	[SEQ ID NO:23]
m35ge-RNA		GAGTGAGAGT GAGGGAACC ACAGGACCAG GAGACGCAGG AGTGGAGCAT	[SEQ ID NO:25]
m35-dRNA		[SEQ ID NO:19]
m35-frNA		GAGAACTTGA ACAAGAAGGT GGTGCTCTGG GCTCTGTAC ACACATCTGG	[SEQ ID NO:21]
m35-aRNA		[SEQ ID NO:15]
m35c1RNA		[SEQ ID NO:17]
	150		
m35-hRNA	101	GTCCTCACAG GGTCTGACA TCTGTGTC AACAAGACAT GAGAGGAGAC	
m35ge-RNA		GTAGCCTGTT CTGCTGGCA GGCTCCACCA AGGTGACCCG GTGTGAGAAG	
m35-dRNA		
m35-frNA		ATTCCAGCAG CGACCTGGAG TTTTCTGGAG ACAGTACCCA GTGAG.GCAG	
m35-aRNA		AAGCTCAGAA GAGTCCCAA TTGCAGGCAA CTGCAGTGT CAGCACCCAC	
m35c1RNA		
	200		
m35-hRNA	151	GACCATGTGG CAGTTCTCTG CTCTACTCCT ATTCTTCCTC CCAGGCTGCT	
m35ge-RNA		ATGCATTGT CATGCT.GG TCCCTTTCT CTTCTGGATC ACAGGCTGCT	
m35-dRNA		...ATGTGG CTGTCCCCAG CTTTGCTTCT TCTCAGTTT CCAGGCTGCC	
m35-frNA		GAGGATGAGG CTATGTGCAG GTCTGCTCCT TCTCTGCTTC CAAGGTTGTT	
m35-aRNA		CATGAGGCCCT CTGGTCCCTG TATGGGCTG CCTGGTGCTC CCAGGTTAT.	
m35c1RNA		GCTGCCCCACG CTGTGTGCTG TGCTGCTGCT TTTTGGCTT CCAGGCTGT.	

Figure 5 (continued)

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m35-hrNA	GCACGGCTCA	GGATTGAGTC	ACAGGTCCAG	AGGAGGTGAG	CGGTCCAGGAG	[SEQ ID NO:23]
m35ge-RNA	GCACGGCTGA	GGATCCAGTC	ACAGGTCCAG	AGGAGGTGAG	CGGTCCAGGAG	[SEQ ID NO:25]
m35-dRNA	TC.....TCCATC	CAAGGCCCCAG	CATTGGTGAG	GGGTCCAGGAG	[SEQ ID NO:19]
m35-frNA	T.....	...GTCTCTG	ACGGGCCCTG	GCTCTGTGTC	TGGCTACGTA	[SEQ ID NO:21]
m35-aRNAGAAGCCCTG	AAGGGTCCAA	AGGAGATCAG	TGGATTGAA	[SEQ ID NO:15]
m35c1RNAGTCCCTCTG	CATGGTCCCA	GCACCATGAC	AGGAAGTGTG	[SEQ ID NO:17]
m35-hrNA	CAGGGCTCCT	TGACAGTGCA	GTGCAGATAT	TCCTCATACT	GGAAGGGTTA	
m35ge-RNA	CAGGGCTCCT	TGACAGTGCA	GTGCCGATAT	ACCTCAGGCT	GGAAGGATTA	
m35-dRNA	CAGGGGTGAG	TGACTGTGCA	ATGTCGCTAT	AGCTCAAGAT	GGCAAACCAA	
m35-frNA	GGAGGCTCTC	TCCGTGTGCA	GTGTCAATAT	AGTCCATCAT	ATAAGGGCTA	
m35-aRNA	GGTGACACCG	TGTCCTCTCG	GTGTACCTAC	GTGGAGAAGA	TGAAGGAGCA	
m35c1RNA	GGTCAATCCC	TGAGTGTGTC	GTGTCAGTAT	GAGGAGAAAT	TTAAGACTAA	
m35-hrNA	CAAGAAGTAC	TGGTGCCG..	.AGGAGTTCC	TCAGAGATCA	TGTGATATTC	
m35ge-RNA	CAAGAAGTAC	TGGTGCCA..	.AGGAGTTCC	TCAGAGATCA	TGTAAGACTC	
m35-dRNA	CAAGAAGTGG	TGGTGCCG..	.GGGAGCAAG	CTGGAGCACT	TGCAGGGTCC	
m35-frNA	TATGAAATAC	TGGTGCCG..	.AGGACCGCA	TGACACGACG	TGTAAAACTA	
m35-aRNA	CAGGAAGTAT	TGGTGCCCGC	AGGGTGGCAT	CCTGGTGTCA	CGCTGCGGTG	
m35c1RNA	GGACAAATAC	TGGTGC....	..AGAGGGTC	ACTTAAGGTA	CTGTGCAAAG	

Figure 5 (continued)

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m35-hRNA	351	TTGTTGAAAC	CGATAAATCA	GAGCAGCTGG	TGAAGAAGAA	CCGTGTGTCC	[SEQ ID NO:23]
m35ge-RNA		TTGTTGAAAC	CGATGCATCA	GAGCAGCTGG	TGAAGAAGAA	CCGTGTGTCC	[SEQ ID NO:25]
m35-dRNA		TCATCCGATC	CACCTGGTCA	GAGAAAGAAA	CGAAGAGCGG	CCGGCTGTCC	[SEQ ID NO:19]
m35-frNA		TTGTAGAAAC	CGACGGAAGT	GAGAAAGAAA	AGAGGAGTGG	CCCAAGTGTCC	[SEQ ID NO:21]
m35-aRNA		ACATTGTCTA	CGCAAATCAG	GACCAGGAGG	TGACTCGAGG	CAGGATGTCC	[SEQ ID NO:15]
m35c1RNA		ATATTGTCAA	GACCAGCAGC	TCAGAAGAAG	CTAGGAGTGG	CAGAGTGACC	[SEQ ID NO:17]
m35-hRNA	401	ATCAGGGACA	ACCAGAGAGA	CTTCATCTTC	ACAGTGACCA	TGGAGGATCT	
m35ge-RNA		ATCAGGGACA	ACCAGAGAGA	CTTCATCTTC	ACAGTGACCA	TGGAGGATCT	
m35-dRNA		ATCAGGGACA	ATCAGAAAAA	TCACTCATTC	CAGGTTACCA	TGGAGATGCT	
m35-frNA		ATCAGAGACC	ATGCTGCGAA	CTCCACCATC	ACAGTGATCA	TGGAGGACCT	
m35-aRNA		ATCCGAGACA	GTCCCCAAGA	GCTCTCGATG	ACCGTGATCA	TGAGGGACCT	
m35c1RNA		ATCAGGGACC	ATCCAGACAA	CCTCACCTTT	ACAGTGACCT	ATGAGAGCCT	
m35-hRNA	451	GAGGATGAGC	GATGCTGGCA	TTTACTGGTG	TGGAATTACG	AAAGTGGAC	
m35ge-RNA		GAGGATGAGC	GATGCTGGCA	TTTACTGGTG	TGGAATTACG	AAAGTGCCAA	
m35-dRNA		CAGGCAAAAT	GACACGGACA	CTTACTGGTG	TGGTATTGAA	AAGTTCGGAA	
m35-frNA		TAGCGAAGAC	GATGCTGGGT	CTTACTGGTG	CAAGATTCAG	A.....	
m35-aRNA		TACCCCTGAAG	GATTCAGGGA	AGTACTGGTG	TGGGATTGAC	AGACTGGGCC	
m35c1RNA		CACCCCTGGAG	GATGCAGACA	CCTACATGTG	TGCGGTGGAT	ATATCACTTT	

Figure 5 (continued)

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m35-hRNA	501	CTGATCCCAT	GTTTAAAGTT	AATGTGAACA	TTGACCAAGC	CCCAAAAAGT	[SEQ ID NO:23]
m35ge-RNA		CCATGCCCCC	CATCACTCC	ACCACCACCA	TCTTCACAGT	GACAACCACA	[SEQ ID NO:25]
m35-dRNA		CTGACCGTGG	GACCAGAGTT	AAAGTGAACG	TCTACTTCGG	CCATATGCAG	[SEQ ID NO:19]
m35-frNA	CTT	CCTTTATCTG	[SEQ ID NO:21]
m35-aRNA		GCGATGAGTC	TTTGTGAGGTT	ACACTCATTG	TCTTTCAGG	GAGCTCCCGT	[SEQ ID NO:15]
m35c1RNA		TTGATGGCTC	.CTTGGGGTT	CGATAAGTAC	TTCAAGATTG	AGTTGTCTGT	[SEQ ID NO:17]
m35-hRNA	551	TCAATGATG.ACCA	CCACAGCCAC	A.GTTCTGAA	ATCCATACAA	600
m35ge-RNA		GTAAAAGAG.ACCAGC	A.TGTTTCCA	ACGCTGACTA	
m35-dRNA		ACCTTCTTC.AGTT	CAGCAGCCAC	ACTGACTCCT	GAGAGGGCAG	
m35-frNA		GGATTCTGTG.GTCA	CGTGATCCAT	CGGTCAGCGT	AAGGTGAAT	
m35-aRNA		CCAGTCGTCT	GGCTGCCCT	TACCACACCA	CAGGACTCCA	GGGCTGTAGC	
m35c1RNA		GGTTCCAAGT	GAGGACCCAG	GACCAACACT	AGAGACACCT	GTGGTGTCCA	
m35-hRNA	601	CCAAGCGCTG	AGAACACTGG	CAAGGAACAA	GTGACTCAGA	GCAAAGAAGT	650
m35ge-RNA		GCTACTACTC	TGATAACGGG	CATGGCGGTG	GTGACAGTGG	CGGTGGTGAA	
m35-dRNA		CAGAGATGTG	GGTAAAGATA	CCATGTCGAC	TTCTAATCAA	CTTCCCTGGC	
m35-frNA		GTTTTTCCAG	TGAATTCTGG	GCAGAACCTG	AGGATTAGTA	CTAATGTGAT	
m35-aRNA		CAGCAGTGTC	TCCAAGCCCC	GTGTGTCCAT	CCCGATGGTC	CGCATGATGG	
m35c1RNA		C....CAGTC	TGCCTACCAA	GGTCCCGCC	CTAGGATCCA	ACACAGAGGA	

Figure 5 (continued)

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m35-hRNA	651	GACTCAGAGC	AGGCCCCACA	CCAGGTCCCT	GCTGAGCAGC	ATCTACTTCC	[SEQ ID NO:23]
m35ge-RNA		GATGGCGTCG	GTGATGGGTT	TCTGGATCTC	AGTGTGCTCC	TCCAGTCAT	[SEQ ID NO:25]
m35-dRNA		CCACTGTGGA	CGGCAGTACA	GACATGGTGT	CTTCTGACTT	GCAGAAGAGG	[SEQ ID NO:19]
m35-frNA	GTTT	ATCTTCCAAC	TGTGTTCCCT	GCTCAGCAGC	ATCCAGTTCC	[SEQ ID NO:21]
m35-aRNA		CCCCAGTCCT	GAT.ACTCTT	GTCCCTGCTG	TTGGCTGCAG	GACTAATTGC	[SEQ ID NO:15]
m35c1RNA		CCGCCGTGAG	CATGACTATT	CCCAGGGCTT	GAGGCTCCCA	GCGCTGTTGT	[SEQ ID NO:17]
m35-hRNA	701	TGCTGATGGT	CTTTGTGGAG	TTACCCCTGC	TCCTGA....	GCATGCTC	750
m35ge-RNA		CTCTGCAG..	..TCCTGTTG	CTTCTCCTGT	TGGTGG....	..CTCGCTC	
m35-dRNA		ACTTGAAGCC	AGTCTAGTTG	GGGCCCTTGT	GGTGGGCTG	ATGCAAGTTC	
m35-frNA		AGGTCCCTGGT	CTTCCCTGAAG	CTGCCCTCTGT	TTCTGA....	..GCATGCTC	
m35-aRNA		CTTTGGCAG.	...CCACATG	CTCCGGTGGG	GAAAGAAAGC	TTGGCTGGCC	
m35c1RNA		CTGTGTTAGC	TCTCCCTGCTG	TTTCTGTTGG	TGGGACCTC	TCTGCTGGCC	
m35-hRNA	751	AGTGCTGTCC	TCTGGGTGAC	CAGGCCTCAG	AGATGCTTTG	GGAGAGGTGA	800
m35ge-RNA		TTTGCTTGGG	GGATGGTGAG	GAGACAGAAG	A.....	.AAGACCTGT	
m35-dRNA		CTTCCCTGTT	TCTGGCCGTC	GCCATCTTTA	CCTTCGTGCT	AACACTGACT	
m35-frNA		TGTGCTATCT	TCTGGGTGAA	CAGACTTTAG	GGGTTCCCTG	GGGGCAATGT	
m35-aRNA		ACAGAGACAC	AGAAGAACGA	GAAGTCTAC	CTTGAAACCT	CGCTGCCAGG	
m35c1RNA		TGGAGGATGT	TCCAGAAAGC	GCTGGTCAA.	AGCTGATAGG	

Figure 5 (continued)

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	850		
m35-hrRNA	AAATGACCTG GTGAAGACCC ATAGTCCTGT TGCCTAGGAT AGAGAGAAAC	[SEQ ID NO:23]	
m35ge-RNA	CCCTGAAGCA GCCAGAACC TCCCCTGGCT CCTCTTGGAA AAAGGGCTCC	[SEQ ID NO:25]	
m35-dRNA	CCTCCTAGTT CCCAGGAAGC ACACAGCACA CCGTCATCAC ACTCAGCCCC	[SEQ ID NO:19]	
m35-frNA	AGAGTGACCC ATCCAAGAAC TATGAAGTGA AGCATCCCA. GGAATGCCCT	[SEQ ID NO:21]	
m35-aRNA	GAACGGCTGG ACCACTGAAG ACTCGACGAT AGACCTTGCA GTGACTCCTG	[SEQ ID NO:15]	
m35c1RNA	CATCCAGAGC TGTCCAGAA CCTCAGACAG GCTTCTGAGC AGAATGAGTG	[SEQ ID NO:17]	
	851		
m35-hrRNA	AGTTCCCAAG AAATGGAAA TAATCTCTGT CTCTCTGTG TCTCTGTCTC		900
m35ge-RNA	TCCATGTCTT CCTCTGGCAA GGACCACCAA GAGGAAGTGG AATATGTAC		
m35-dRNA	AGTGGCTTCC AAGGAAGAGA TGAACCGTCT CTCTCAA... ..		
m35-frNA	GGGAGGAAC CAGTCTCTGCA TGCAGACTGG ACTTCATTGT TCTGTGTCTC		
m35-aRNA	AATGTCTCAG AAACCTCAAC CCTTCTGCTG TGCCCTCTCC TGAGACACAG		
m35c1RNA	CCAGTATGTG AATTGCGAG TGCACAGTG GTCTCTGAGG GAAAGAGCCG		
	901		
m35-hrRNA	..TGCTCTG GGGTGTATGT ATGTGTGTGC ATGCACCTTG CCGGGGCAGA		950
m35ge-RNA	CATGGCTCCC TTTCCAGGG AGGAGTTTC ATATGCCGCT CTGACTTTGG		
m35-dRNA		
m35-frNA	A.....		
m35-aRNA	AAC..CTCAG TCAGTCTACA GAGGAGGAAG AGGCAGCTCG TTCCCTGGAC		
m35c1RNA	TGCTACCAAG TCAGGTAGAA GTGGTGAAT ATAGCACATT GGCAATTACCC		

Figure 5 (continued)

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m35-hRNA	951	1000	[SEQ ID NO:23]
m35ge-RNA			[SEQ ID NO:25]
m35-dRNA			[SEQ ID NO:19]
m35-frNA			[SEQ ID NO:21]
m35-aRNA			[SEQ ID NO:15]
m35c1RNA			[SEQ ID NO:17]
m35-hRNA	1001	1050	
m35ge-RNA			
m35-dRNA			
m35-frNA			
m35-aRNA			
m35c1RNA			
m35-hRNA	1051	1100	
m35ge-RNA			
m35-dRNA			
m35-frNA			
m35-aRNA			
m35c1RNA			

Figure 5 (continued)

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1101	1150
m35-hRNA	[SEQ ID NO:23]
CATACACGAG	TGCCCTAGCT TAAAAACAAA CAAACAAACA AACACCTTAG
m35ge-RNA	[SEQ ID NO:25]
GCGGCTTGA	GATGGATCT TTACATCTGC CTCTGTACCT GCTTCCTTAC
m35-dRNA	[SEQ ID NO:19]
.....
m35-frNA	[SEQ ID NO:21]
.....
GTTTCTACTC	ACAGTCCACG GCTCTGTCCA CCTTCCTTCC GGCTCTCTTT
m35-aRNA	[SEQ ID NO:15]
CCTGTGACTC	CTTGTACCT GATCCTCTCA GTGGTGACTA CCAGGTTCCA
m35c1RNA	[SEQ ID NO:17]
1151	1200
m35-hRNA	GTTG..... TAGGATTGA ACTCATGTCC TTGTACCTGC AAGGAAGGTA
m35ge-RNA	CCGGCCCCAGC TGGTGACTGG AACTCTGTCC ATCCGTCTCT CATGGCCATC
m35-dRNA
m35-frNA
CATGCCCCAG	ATGGAGAGT GTCTTGGTCC CTGAAGCCCG GATGGTACTT
m35-aRNA	AGGCTCCCTG CTGGCTGCTG CCCTCAATGT CATGAGCCTC AGTGGCTTCA
m35c1RNA	
1201	1250
m35-hRNA	GCGGATTAC CTGCTGAGCC ATCTCCCCAA TCTGGAGAAG ACTCAATCTA
m35ge-RNA	AGCTCTACCT TGCTTGAGCT TGGAGTTCAA CCTCAGGGGG TTCCAGGGAA
m35-dRNA
m35-frNA
AACAAGTCCA	GCCAGAGGCT GGAACCT.CC CGCATATTCT AATCCCTGGG
m35-aRNA	CTAAAGATGA GCAGGAGCCA GGGCTCTGTG GGCACAGTCT CATCCCACCTG
m35c1RNA	

Figure 5 (continued)

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	1251		1300	
m35-hRNA	GTAAGAACA	ACTCATCAGC	AGTACCATGG	CTCTGATGTG
				[SEQ ID NO:23]
m35ge-RNA	TTAAGGCTCC	TTCCACATCC	CCAATTATAG	CCAATGTACC
				[SEQ ID NO:25]
m35-dRNA
				[SEQ ID NO:19]
m35-frNA
				[SEQ ID NO:21]
m35-aRNA	AAGAGTTAAT	GGGTGTGTGG	GCCTTCATCG	GGGCTGGCC
				[SEQ ID NO:15]
m35c1RNA	GCTCTCTCCT	CTTAGCCTGT
				[SEQ ID NO:17]

	1301		1350	
m35-hRNA	AGACTCAGAC	TAATCCCACT	CCTATAGCAG	GGACAGCTGA
				GTTCTGGAAC
m35ge-RNA	CCAGGCAGGC	TGCTTCAGGG	ATGCTGTGTA	AATCGTATCA
				ACGATGACAA
m35-dRNA
				[SEQ ID NO:19]
m35-frNA
				[SEQ ID NO:21]
m35-aRNA	GATAAAGGCT	GAGTTTGTGT	GCGTTCCAGG	AAATCCCTG
				GGCATGGATG
m35c1RNA
				[SEQ ID NO:17]

	1351		1400	
m35-hRNA	CCATTTCATGT	GCCCCCTCTCT	CAGGACATCC	TGCAATACCT
				ATCTGGGGCT
m35ge-RNA	TAATAGCAAT	CAACCTTTAT	TTAT.....
				[SEQ ID NO:19]
m35-dRNA
				[SEQ ID NO:21]
m35-frNA
				[SEQ ID NO:23]
m35-aRNA	TCCAGCAACA	GTCCACCTC	CCATCCTCGG	AAGATCCCAC
				CTTCACCTCC
m35c1RNA
				[SEQ ID NO:17]

Figure 5 (continued)

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	1401		1450	
m35-hRNA	ATCTTCCACT	GATGACTTCC	AAAGAAGAAA	ATACAAGAAA ACATCACATT [SEQ ID NO:23]
m35ge-RNA [SEQ ID NO:25]
m35-dRNA [SEQ ID NO:19]
m35-frNA [SEQ ID NO:21]
m35-aRNA	CTCTAATTCT	TCTGCATCAA	TTGCTATGGA	GGAGACAACA TATGTGTGTC [SEQ ID NO:15]
m35c1RNA [SEQ ID NO:17]
	1451		1500	
m35-hRNA	TCTTCTTAGT	GTACTAGTTC	CTTAGAGGAC	ACATGCCAAT ATAAGACTGC
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	TATGAAACAC	CTGCATCCTG	GCCTCTTAGA	AAATAATTAA AACAAATTC
m35c1RNA
	1501		1550	
m35-hRNA	GGGCCACCAG	CCAGTTGATT	GACCAAATAT	CTCGGTGATG TGGCCTCACC
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	TGCAGACCCA	TCAAGACTCA	CCAAACCATC	TCTAGGGCAG GGCCTGGGAC
m35c1RNA

Figure 5 (continued)

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1551		1600	
m35-hrNA	AAGTAGCATA AAGTTTGCCA CTGTCACACT AGCTATCTGT CCCTTATTGG		[SEQ ID NO:23]
m35ge-RNA		[SEQ ID NO:25]
m35-dRNA		[SEQ ID NO:19]
m35-frNA		[SEQ ID NO:21]
m35-aRNA	TCCACAGTTC TGACAAGTGA CCTGGCCATT CCTACCCCTTG GGTCTGATGA		[SEQ ID NO:15]
m35c1RNA		[SEQ ID NO:17]
1601		1650	
m35-hrNA	CAGGACACAC CCTGCTTTCT TTTTCTCAA CACAGCCCAG TGACTAAGCC		
m35ge-RNA		
m35-dRNA		
m35-frNA		
m35-aRNA	ATCCTCAGCC CATTTAGCT AGAATCTTCC TTCCCTTCCTT CCTTCCTTCC		
m35c1RNA		
1651		1700	
m35-hrNA	CATTGCAAAC CCAGATGGAG TAGTTGACCT AAGCTTTGTA CCACCTGCTC		
m35ge-RNA		
m35-dRNA		
m35-frNA		
m35-aRNA	TTCCTTCCTT CCTTCCTTCC TTTCCTTCCT TTCCCTTCCTT TCCTTCCTTT		
m35c1RNA		

Figure 5 (continued)

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	1701		1750	
m35-hRNA	AGGTCCTTCAA	GTAGTAGTTA	AGCCTTGGTC	CCTGAAATCT AGATTGCTCA [SEQ ID NO:23]
m35ge-RNA [SEQ ID NO:25]
m35-dRNA [SEQ ID NO:19]
m35-frNA [SEQ ID NO:21]
m35-aRNA	CCTTCCTTTC	CTTCCCTTTCT	TCGTTCCCTTC	CTGCCCTCCC TGTGGGGTTT [SEQ ID NO:15]
m35c1RNA [SEQ ID NO:17]
	1751		1800	
m35-hRNA	GTGAGACCAA	ATGGGGAGGT	CAACTGCAGG	AATCAGCTGA TCTCACAGGA
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	CCTATATGCT	TCCTAGACCT	AGATCATGAC	AGTACGGTCC CAGTAGGCAC
m35c1RNA
	1801		1850	
m35-hRNA	GTCACGAACC	CACATCACCC	CCAAACCCCTT	CCAGGAATGG TCTCTTCACC
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	TTCCTGATGC	CTCTCTGGTC	AGGCACACTA	TGGTGACAGC CAGCCCAAGG
m35c1RNA

Figure 5 (continued)

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	1851	1900	
m35-hRNA	AGGCCCTTCC ACTCTCTCCC TTTTACTCAG ACAAAATCTAT TGAATGTCTA	[SEQ ID NO:23]	
m35ge-RNA	[SEQ ID NO:25]	
m35-dRNA	[SEQ ID NO:19]	
m35-frNA	[SEQ ID NO:21]	
m35-aRNA	CAGCCAGGGA TCAGCTGTCT CTCCATCCTC CTTCCCCAAG GCCCTGTGTC	[SEQ ID NO:15]	
m35c1RNA	[SEQ ID NO:17]	
	1901	1950	
m35-hRNA	AGTAGTTATC ACTCTCCACA TACATGCTCC AAAATAAGAC AGACCCAATT		
m35ge-RNA	
m35-dRNA	
m35-frNA	
m35-aRNA	CCTTGCTTTG GTAGGACACT GGAGGAAGTC TCGATATCAT TCCTGTCCAG		
m35c1RNA	
	1951	2000	
m35-hRNA	AAAGTCCATA GAGAAGGCCA ATGGGATCAA AGGTAAATAC TCAGGGGAAA		
m35ge-RNA	
m35-dRNA	
m35-frNA	
m35-aRNA	AGTGGTTACT CCTCCATGGG GTCTGGAGGC TGAGGGAGAG GAGGAGGAGG		
m35c1RNA	

Figure 5 (continued)

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	2001	2050	
m35-hRNA	TGAGTAGTCT	CAGCCACCA GTCTCAGACA TCCTGAGTTC TGCACCATGA	[SEQ ID NO:23]
m35ge-RNA	[SEQ ID NO:25]
m35-dRNA	[SEQ ID NO:19]
m35-frNA	[SEQ ID NO:21]
m35-aRNA	AGGATACCAAG AGTGGGAAGG GGGCGGGGA AACAGAAGAC ACTAGACTCT		[SEQ ID NO:15]
m35c1RNA	[SEQ ID NO:17]
	2051	2100	
m35-hRNA	CACAGTCTTC TTCTTGAGTG GGGCTCTGAC ACCACAGCC AAATTCACAA		
m35ge-RNA	
m35-dRNA	
m35-frNA	
m35-aRNA	AGTTACTAGA GGAGAATACT AAATCCAGTA CTGTTGAGTG AGGAAAGAT		
m35c1RNA	
	2101	2150	
m35-hRNA	CTAACATGGG TGTCTCTCAA CTTTGTGGAA GAAGAGTCCC CAGTTAGCA		
m35ge-RNA	
m35-dRNA	
m35-frNA	
m35-aRNA	GGA CTGGCTC AACTATTTT TTTCCTTTT CTATTTGTT TTGAAAAGTA		
m35c1RNA	

Figure 5 (continued)

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2151	2200
m35-hrNA	TCTTCTCAGT GATGACATGT GTTGGACTCT AGTGAGCTTG CCTCTTGTTA [SEQ ID NO:23]
m35ge-RNA [SEQ ID NO:25]
m35-dRNA [SEQ ID NO:19]
m35-frNA [SEQ ID NO:21]
m35-aRNA	AGATGTTGGG AAGGAGGTG TTCAGAATAT AAACAGAAA TGTAGGAGAGA [SEQ ID NO:15]
m35c1RNA [SEQ ID NO:17]
2201	2250
m35-hrNA	AGAGGATGGT TTTCATTGC TTCAGGGGTA TACCTGCCAG TCAGTCAGCC
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	ATACAAAAGA AGTGCTGTTT CTAGGATCAT ATATAACCTC ACCAAACCTT
m35c1RNA
2251	2300
m35-hrNA	ACATTCCCAC TCATGCTCAG ACCAACAATC ATGGTTAAAC TCTGTGGGAC
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	GTTGACGGCT CTGCCCTGAGC TTGCAGGACC CCCCTCCCTT CCCCTCCCTT
m35c1RNA

Figure 5 (continued)

	2301	2350	
m35-hRNA	ACACACACAC ACACACACAC ACACACACAC ACACACACAC GACATATAAT		[SEQ ID NO:23]
m35ge-RNA	[SEQ ID NO:25]
m35-dRNA	[SEQ ID NO:19]
m35-frNA	[SEQ ID NO:21]
m35-aRNA	TCCAGTATTT GCAGATGCTC CGTTTACAGA GGGGTCCTCT CACCATGCAC		[SEQ ID NO:15]
m35c1RNA	[SEQ ID NO:17]

	2351	2400
m35-hrRNA	CAGGAGAGGG ACTCATTAGA GCCTGTAGGT CAGGCAGTGG TAGCACATGC	
m35ge-RNA
m35-dRNA
m35-fRNA
m35-aRNA	AGCCCACTAC GCATCACACG CTGTCTCGTC ATAAGCATCC CTCGGTGTTC	
m35c1RNA

	2401'		2450
m35-hrNA	CTTTAAATCTC AACACTCAGG AGGCAGAGGC AGGTGGATTT	CTGAGTTCTA	
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA	TACGAACCTTT GTACAATAAA CTTTCTCAGC TGTGTAGTAT	TT.....	
m35c1RNA

Figure 5 (continued)

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2451	GGTCAGTCTG	CTTTACAGAG	TGAGTTCTAG	GACTACACAG	AGAAATCCAA	2500	[SEQ ID NO:23]
		[SEQ ID NO:25]
m35-hRNA		[SEQ ID NO:19]
m35ge-RNA		[SEQ ID NO:21]
m35-dRNA		[SEQ ID NO:15]
m35-frNA		[SEQ ID NO:17]
m35-aRNA		
m35c1RNA		

2501	AAAAACAAGG	CTACACAGAG	AAACCATGTC	CTGGGGTAAA	AAAGAAAAAG	2550
m35-hRNA	
m35ge-RNA	
m35-dRNA	
m35-frNA	
m35-aRNA	
m35c1RNA	

2551	AAAA
m35-hRNA
m35ge-RNA
m35-dRNA
m35-frNA
m35-aRNA
m35c1RNA

Figure 5 (continued)

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m35eIg-aaGCCTAQD	PVTGPEEVSG	QEQGSILTVQC	[SEQ ID NO:27]
m35h-aa	MWQFSALLLF	FLPGCCTAQD	SVTGPEEVSG	QEQGSILTVQC
m35ge-aaM	HLSLVPPFLF	WITGCCTAED	PVTGPEEVSG	QEQGSILTVQC
m35f-aa	MRLCAGLLLL	CFQGC...L	SLTGPGSVSG	YVGGSLRVQC
m35d-aa	MWLSPALLLL	SFPGC...L	SIQGPALVRG	PEQGSILTVQC
m35c-aa	MTQLASAVWL	PTLLLLLLLL	WLPGC...V	PLHGPSTMTG	SVGQSLSVSC
m35a-aaMRPLVLL	WGCLVLPGYE	ALKGPKEISG	FEGDITVSLRC
51					
m35eIg-aa	RYDSGWKDYK	KYWC...GAY	WKSCEILVET	DASEQLVKEN	RVSIRDQDQTD
m35h-aa	RYSSYWKGYK	KYWC...GVP	QRSCDILVET	DKSEQLVKKN	RVSIRDNQRD
m35ge-aa	RYTSGWKDYK	KYWC...GVP	QRSCCTLVET	DASEQLVKKN	RVSIRDNQRD
m35f-aa	QYSPSYKGYM	KYWC...GPH	DTTCKTIVET	DGSEKEKRSR	PVSIRDHAAN
m35d-aa	RYSSRWQTNK	KWCR...GAS	WSTCRVLIRS	TGSEKETKSG	RLSIRDNQKN
m35c-aa	QYEEKFKTKD	KYWC...GSL	KVLCKDIVKT	SSSEE.ARSR	RVTIRDHPDN
m35a-aa	TYVEKMKHEH	KYWCRRQGGIL	VSRCGDIVYA	NQ.DQEVTRG	RMSIRDSPPQE
101					
m35eIg-aa	FIFTVTMEDL	RMSDADIYWC	GITKA.....	.GTDPMFKVN	VNIDP.....
m35h-aa	FIFTVTMEDL	RMSDAGIYWC	GITKG.....	.GPDPMFKVN	VNIDQAPKSS
m35ge-aa	FIFTVTMEDL	RMSDAGIYWC	GITKV.....	.PTMPPITST	TTIFTVTITV
m35f-aa	STITVIMEDL	SEDDAGSYWC	KIQTSEIWD	WSRDPVSVR	VNVFVNSGQ
m35d-aa	HSFQVTMEML	RQNDTDIYWC	GIEK.....	FGTDRGTRVK	VNVYFGHMQT
m35c-aa	LTFTVTYESL	TLEDADTYMC	AVDISLFDGS	LGFDKYFKIE	LSVVPSEDPG
m35a-aa	LSMTVIMRDL	TLKDSGKYWC	GIDR.....	LGRDESFEVT	LIVFPGSSRP

Figure 6

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151	200	
m35eIg-aa [SEQ ID NO:27]	
m35h-aa	MMTTATVLK SIQPSA.ENT GKEQVTSKE VTQSRPHTRS LLSSYFLL. [SEQ ID NO:24]	
m35ge-aa	KETSMFPTLT SYSDN.GHG GDSGGGEDG VDGFLDLSV LLPVISAVL. [SEQ ID NO:26]	
m35f-aa	NLRISTNVMF IF.....QLWS LLSSIQFQV. [SEQ ID NO:22]	
m35d-aa	FFSSAATLTP ERAAEMWVKI PCRLINFPF PLWTAVQTCW LLTCRRGLEA [SEQ ID NO:20]	
m35c-aa	PTLETVPVST SLPTKGPALG SNTEDRRREHD YSQG.LRLPA LLSVLALLLF [SEQ ID NO:18]	
m35a-aa	VVWLPLTT..PQ DSRVASSVS KPSVSI PMVR MMAPVLILLS [SEQ ID NO:16]	
201	250	
m35eIg-aa	
m35h-aa	.MVFVELPLL LSM.....LSAVLWVT RPQRCFGRGE NDLVKTHSPV	
m35ge-aa	.LLLLLVASL FAWRMVRRQK KDLSLKQPRT SPGSSWKKGKGS SMSSSGKDHQ	
m35f-aa	.LVFLKLPLF LSMLCAIFWV NRL*.....	
m35d-aa	SLVGAFVGG LMQVPSCSLAV AIFTFVLTLT PPSSQEAHST PSSHSAPVAS	
m35c-aa	LLVGTSLLAW RMFQKRLVKA DRHPELSQNL RQASEQNECQ YVNLQLHTWS	
m35a-aa	ILLAAGLIAF GSHMLRWRKK AWLATETQKN EKVYLETSLP GNGWTTEDST	
251	300	
m35eIg-aa	
m35h-aa	A.....	
m35ge-aa	EEVEYVTMAP FPREEVSYAA LTLAGLGQEP TYGNTGCPIT HVPRTGLEEE	
m35f-aa	
m35d-aa	KEEMNRLF*.....	
m35c-aa	LREEPVLPSQ VEEVEYSTLA LPQEEELHYSS VAFNSQRQDS HANGDSLHQP	
m35a-aa	IDLAVTPECL RNLNPSAVPS PETQNL SQST EEEEAARS LD DDKEDVMAPP	

Figure 6 (continued)

301		323
m35eIg-aa	[SEQ ID NO:27]
m35h-aa	[SEQ ID NO:24]
m35ge-aa	TTEYSSIRRP LPAAMP*	[SEQ ID NO:26]
m35f-aa	[SEQ ID NO:22]
m35d-aa	[SEQ ID NO:22]
m35c-aa	QDQKAEYSEI QKPRKGLSDL YL*	[SEQ ID NO:18]
m35a-aa	PLQMSAEELA FSEFISV*	[SEQ ID NO:16]

Figure 6 (continued)

	Spleen	Thymus	Lymph Nodes	Kidney	Liver	Heart	Skin	Bone Marrow	Gut	T lympho- cyte EL4	macro- phage RAW	macro- phage J774	mono/ma- cro P388D1	P815	CD11b (O)	CD11b (M)	B cell CD43R	T cell CD3
m35a	+	+	+	+	+	+	+	+	+									
BALB/c mouse 2																		
cell lines																		
m35c	+++	+++	+++	+++	+++	+++	+++	+++	+++	---	+++	+++	+++	---				
BALB/c mouse 2																		
cell lines																		
m35d								+++										
BALB/c mouse 2																		
cell lines																		
m35e	+	+	+	+	+	+	+	+++	+++		+++	+++						
BALB/c mouse 2																		
cell lines																		
m35f	++	-	-	-	++	-	-	---	-	---	+++	+++	---	---				
BALB/c mouse 2																		
cell lines																		
m35g	+	+	+	+	+	+	+	+++	---	---	+++	+++	---	---				
BALB/c mouse 2																		
cell lines										+++	+++	+++	+++	+++	---	---	---	---

Figure 7

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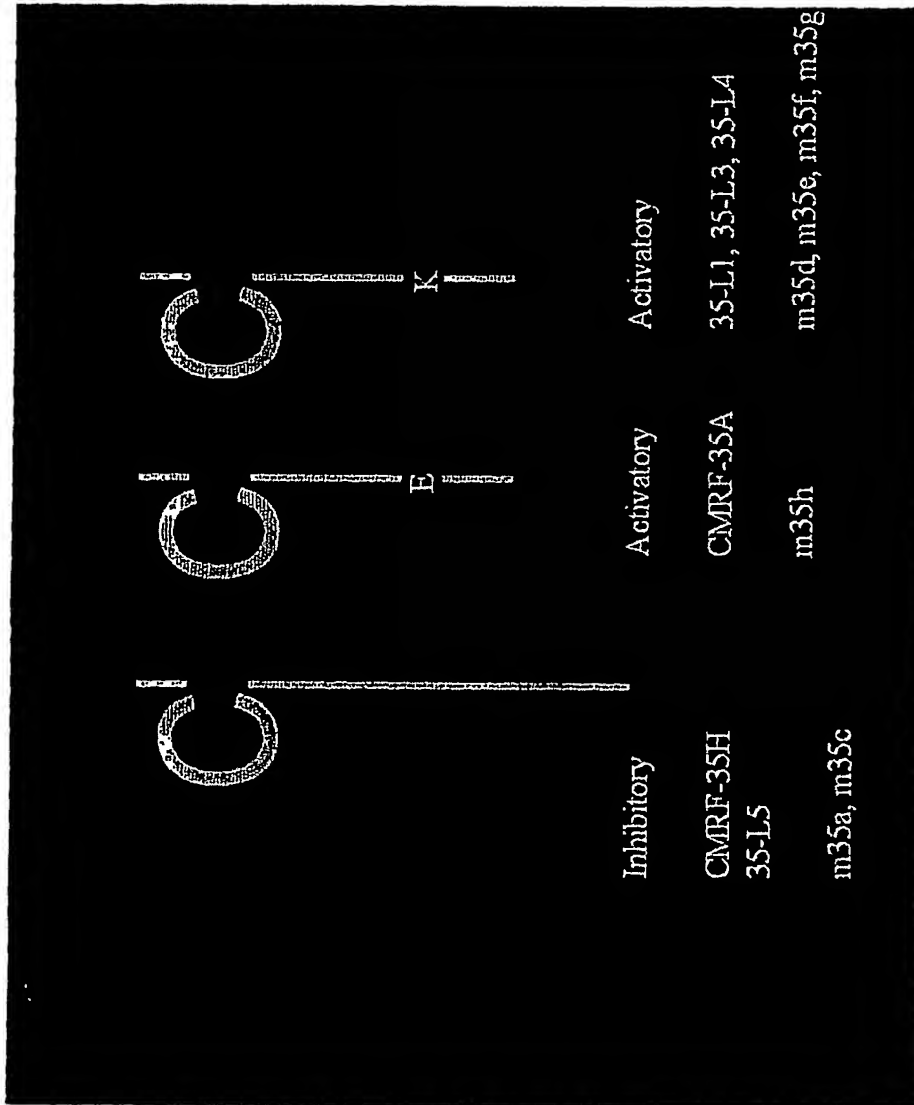


Figure 8

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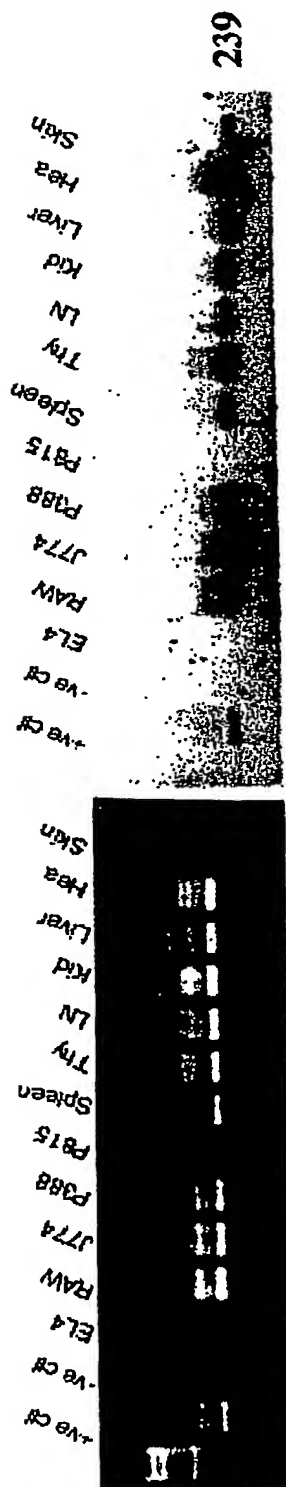


Figure 9A

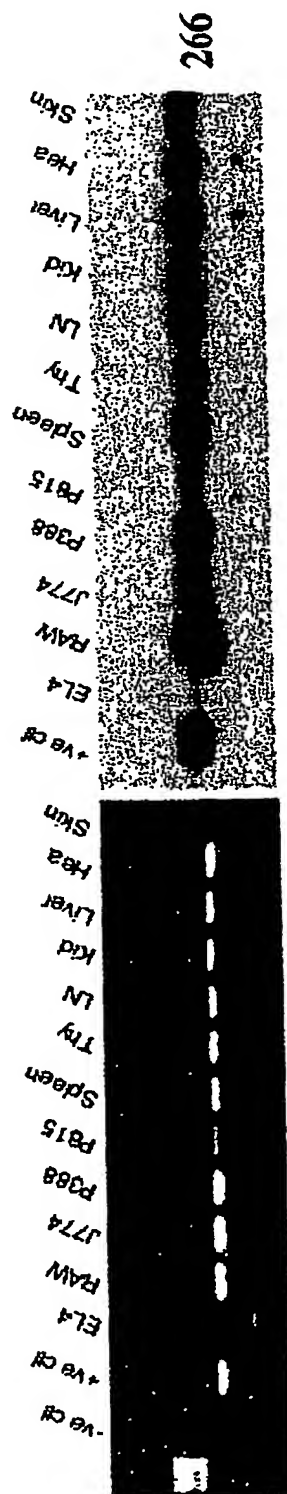


Figure 9B

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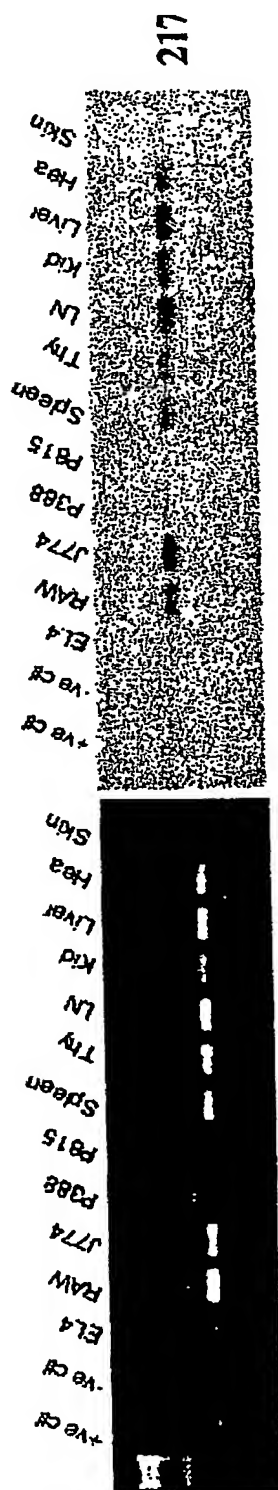


Figure 9C

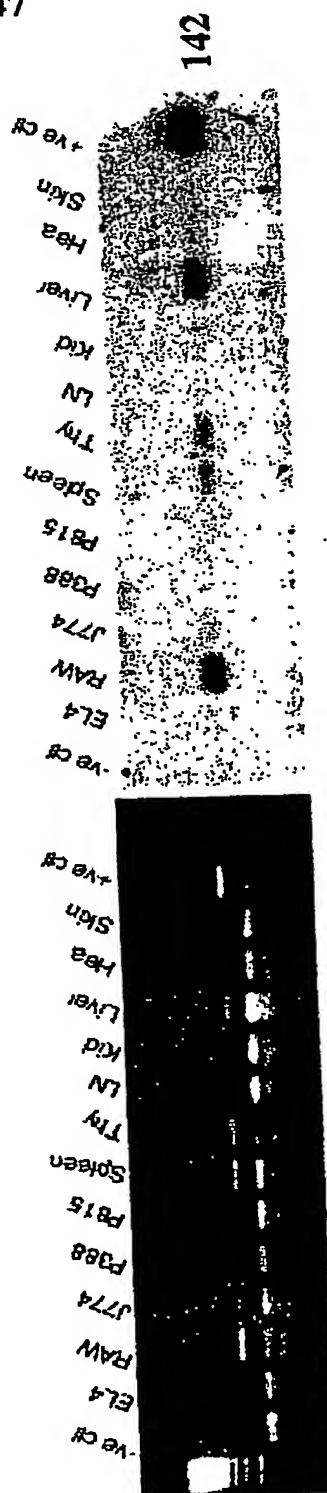


Figure 9D

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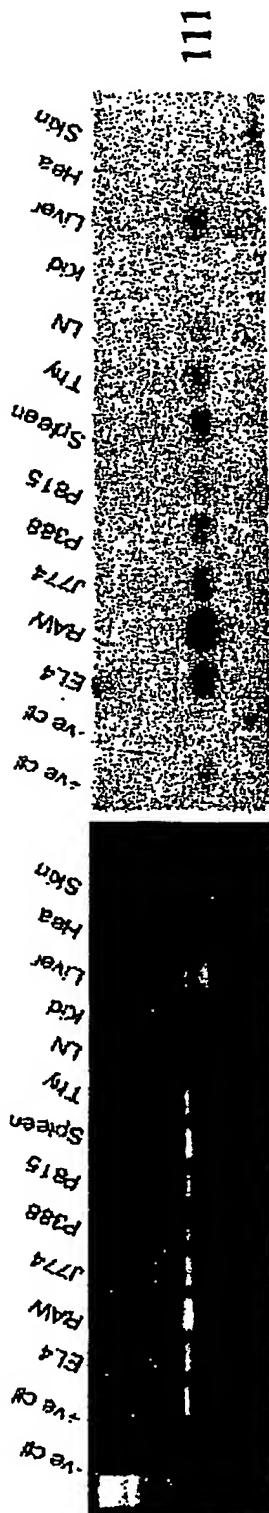


Figure 9E

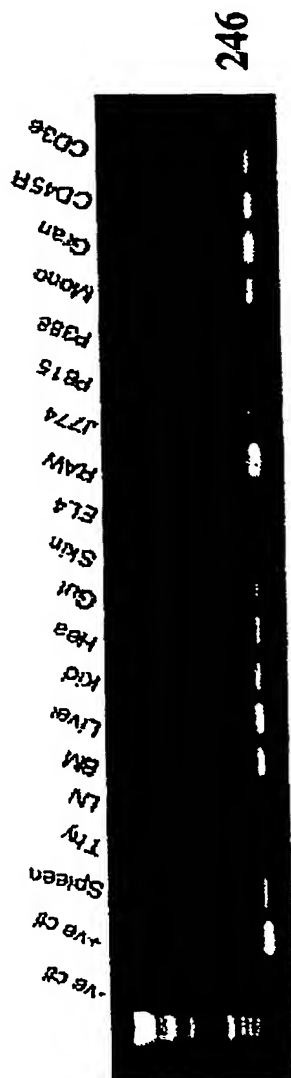


Figure 9F

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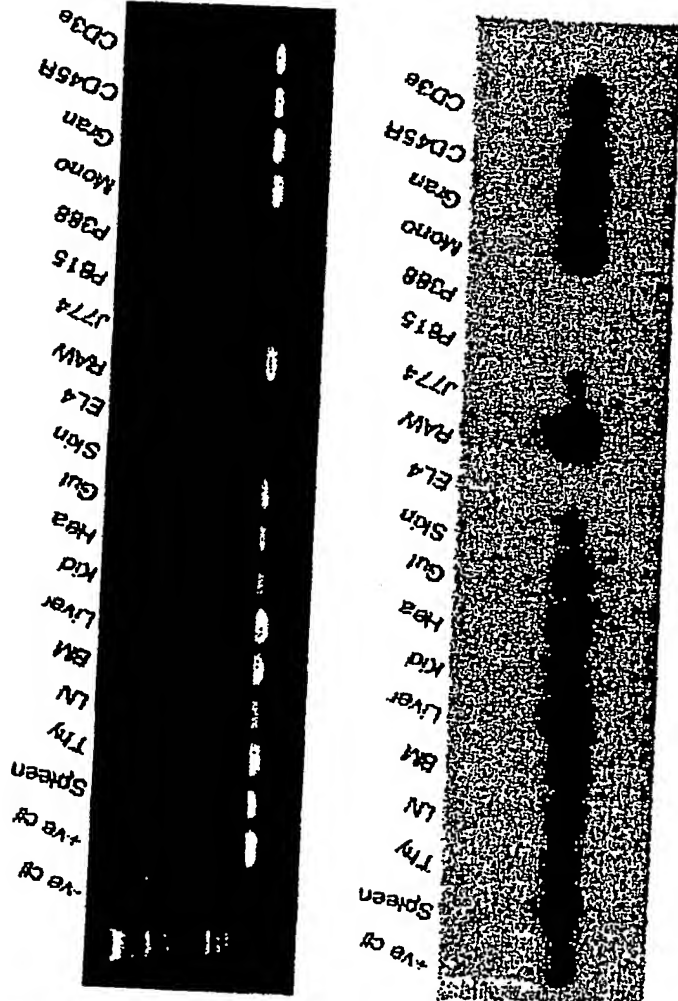


Figure 9G

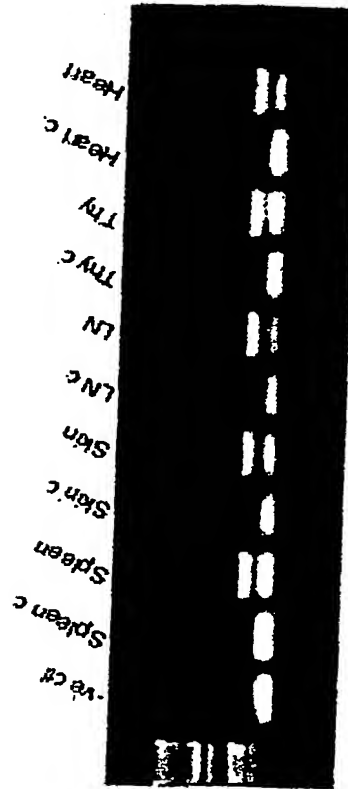


Figure 9H

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